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ORIGINAL RESEARCH

Exploring the Interaction Mechanisms of Antibody-Mediated Immune Responses with Gout and Rheumatoid Arthritis Through a Bidirectional Two-Sample Mendelian Randomization Study

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Purpose: Gout and Rheumatoid arthritis (RA) are two prevalent non-infectious inflammatory joint diseases that can occur independently or concurrently. The effects and mechanisms related to antibody-mediated immune responses and both Gout and RA remain unclear. The research seeks to investigate the potential causal association and offer a novel perspective for their prevention and treatment strategies.

Methods: The study employed the bidirectional two-sample Mendelian randomization (MR) analysis for investigation. Datasets comprising 46 antibody-mediated immune responses, as well as those for Gout and RA, were curated from published genome-wide association studies (GWAS). For the causality analysis, methods such as Inverse Variance Weighted (IVW), Weighted Median, Simple Mode, MR-Egger, and Weighted Mode were utilized. We chose MR pleiotropy residual sum and outlier (MR-PRESSO), IVW, MR-Egger, and Leave-one-out for sensitivity analysis to enhance the reliability of the results.

Results: We meticulously excluded the results that exhibited pleiotropy and instability. Finally, four antibody-mediated immune responses have been found as causal factors in the development of Gout: Anti-chlamydia trachomatis IgG seropositivity, Anti-human herpes virus 6 IE1B IgG seropositivity, Helicobacter pylori GroEL antibody levels, and Polyomavirus 2 JC VP1 antibody levels; Two antibody-mediated immune responses influence RA causally: BK polyomavirus VP1 antibody levels, and Helicobacter pylori Catalase antibody levels. In the reverse analysis, three antibody-mediated immune responses could be influenced by Gout: BK polyomavirus VP1 antibody levels, Chlamydia trachomatis tarp-D F2 antibody levels, and Varicella zoster virus glycoproteins E and I antibody levels; Two antibody-mediated immune responses could be causally affected by RA: Anti-human herpes virus 7 IgG seropositivity, and Merkel cell polyomavirus VP1 antibody levels.

Conclusion: The research indicated that antibody-mediated immune responses establish a causal link with this two non-infectious inflammatory joint diseases: Gout and RA, offering new avenues and perspectives for the future prophylaxis and treatment of diseases from an immunological standpoint.

Keywords: antibody-mediated immune responses, rheumatoid arthritis, Gout, Mendelian randomization

Introduction

RA, a chronic inflammatory autoimmune disorder, impacts approximately 1% of the population globally, predominantly striking the individuals aged between 30 and 50, with a higher incidence among the elderly. The incidence among women is roughly two-three times that of men.[1,2] RA primarily affects joint, leading to persistent inflammation and injury. The pathological features revolve around the joint synovitis, characterized by synovial cell proliferation, fibrosis, the infiltration of inflammatory cells, and formation of pannus, which results in the degradation of bone and cartilage tissues.[3] Symptoms typically manifest as symmetrical joint pain, swelling, stiffness. Additionally, RA can affect various extra-articular tissues and organs, including the heart, blood

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vessels, lungs, kidneys, and gastrointestinal tract.[4,5] Cardiovascular disease represents a major contributor to mortality rates among individuals suffering from RA. A meta-analysis conducted in 2012, encompassing 14 studies and 41,490 patients, revealed that individuals suffer from RA are confronted with a 48% elevated risk of cardiovascular disease.[6] Innate and adaptive immunity are pivotal in the advancement of RA. Dysregulated humoral immunity overactivates T and B lymphocytes. Dendritic cells serve as the primary antigen-presenting cells, playing a crucial role in presenting antigens to T cells and providing co-stimulatory signals to initiate their activation.[7] This contributes to various inflammatory mediators' production, like interleukin (IL)-17A, IL-17F, and IL-22[8]. B cells become hyperactive and produce autoantibodies: anti-citrullinated protein antibodies and rheumatoid factor, which led to the formation of immune complexes and trigger the inflammation.[9]

The key factors driving the development of Gout are the chronic accumulation of monosodium urate (MSU) crystals and hyperuricemia.[10] It is an inflammatory arthritis associated with metabolic and immune factors, with a prevalence ranging from 1% to 6.8%. The number of patients affected is on the rise annually.[11] This is a recurrent, self-limiting condition characterized by symptoms including redness, swelling, pain, and impaired function in one or more joints. It may also involve the formation of tophi, which can result in the deterioration of joint bones and cartilage. In certain instances, it also contribute to the cardiovascular, renal, and various other systemic diseases.[12,13] MSU crystals activate adaptive and innate immunity in the context of hyperuricemia, stimulating macrophages, innate lymphocytes, dendritic cells, T cells, and so forth, which triggers to the activation of the NLRP3 inflammasome and mediates a cascade of inflammatory responses.[14] Gout and RA can manifest either separately or concurrently, exerting a more significant psychosocial impact on patients.

Gout and RA have been confirmed as non-infectious inflammatory joint disorders linked to autoimmunity. These diseases exert significant impacts not only on local tissues but also on the body as a whole, extending beyond the joints. However, certain researches indicated that the incidence of Gout and RA is connected with infections caused by infectious agents such as bacteria or viruses. Xie D[15] discovered that individuals with Gout are at a higher likelihood of contracting SARS-CoV-2 and face a heightened risk of severe complications compared to those without Gout. Porphyromonas gingivalis significantly affects the onset and progression of RA by expressing the peptidyl arginine deiminase enzyme.[16] RA patients exhibited higher titers of EA, EBNA, and VCA antibodies.[17] A meta-analysis that included 5 Chinese studies and 1 American study indicated a positive correlation between autoimmune diseases and an increased risk of COVID-19.[18] Butler-Laporte et al conducted a study utilizing serum samples from 9724 individuals, selecting 13 pathogens for a GWAS.[19] Previous studies on infectious diseases associated with RA and Gout are limited and primarily observational, with the causal relationship between them remaining unclarified. This study innovatively investigates whether other infectious diseases have effects on the pathogenesis of RA and Gout, based on the identified research gap, and discusses how these infectious, antibody-mediated immune responses participate in and influence these two non-infectious diseases.

MR employs genetic variation associated with exposure as an instrumental variable (IV) to infer causal relationships with outcomes, mitigating the impact of confounders and reverse causal bias.[20] MR is more convenient and cost-effective than randomized controlled trials (RCT). It leverages the principle that alleles are randomly allocated during the meiosis, emulating the randomization process of the RCT.[21] To exclude the influence of confounders, we utilized MR to establish a direct association between exposure and outcome. The study is grounded in GWAS datasets, using a bidirectional two-sample MR to explore the causal relationship between antibody-mediated immune responses and the progression of both Gout and RA. The findings are anticipated to offer a more comprehensive understanding of the etiological mechanisms behind Gout and RA, and to provide a novel perspective and direction for the prevention of these diseases.

Methods

Study Design

The study conducted by using the "TwoSampleMR" package in R Studio (2024.09.0+375), R (version 4.4.1), with a significance level of $P<0.05$. We designed a bidirectional two-sample MR analysis process model (refer to Figure 1) to assess the association between the antibody-mediated immune responses and both Gout and RA. First, we designated antibody-mediated immune responses as "exposure", with Gout and RA serving as "outcome". We employed two-sample

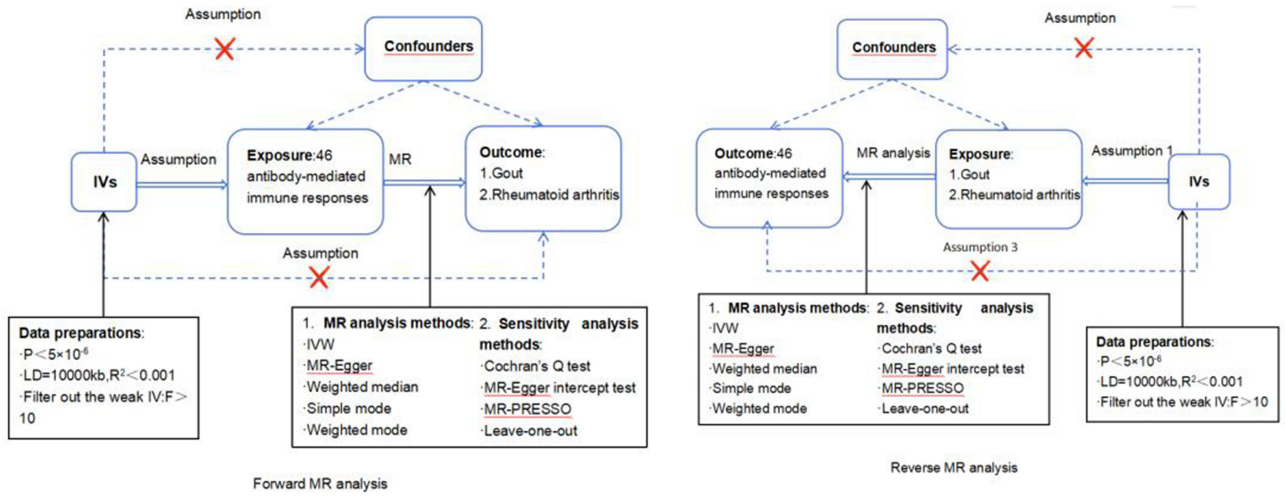

Figure 1 Overall design of the MR analysis.
Abbreviations: IVs, instrumental variable; IVW, inverse-variance weighted; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier; SNPs, single-nucleotide polymorphisms.

MR to analyze the impact of antibody-mediated immune response on Gout and RA. Then, using reverse two-sample MR, we designated Gout and RA to "exposure" and antibody-mediated immune responses to "outcome", to explore the influence of Gout and RA on antibody-mediated immune responses.

Data Sources

The study selected exposure and outcome from different studies based on two different individuals in Finland and the UK to minimize sample overlap and ensure the robustness of the findings. Summary data related to antibody-mediated immune responses were sourced from the GWAS Catalog (https://www.ebi.ac.uk/gwas/) (accessed on November 8, 2024). Butler-Laporte et al utilized the UK Biobank to perform serologic measurements on 9724 adults of European descent, selecting 13 pathogens for 46 GWAS (GWAS ID: GCST90006884 to GCST90006909) [18]. The datasets for RA (finngen_R11_M13_RHEUMA) and Gout (finngen _ R11 _ M 13 _ Gout) are from the FinnGen biobank analysis round 11 (https://www.finngen.fi/en) (accessed on November 9, 2024). Gout is characterized by " A condition characterized by painful swelling of the joints, which is caused by deposition of urate crystals". RA is described as "A chronic, systemic autoimmune disorder characterized by inflammation in the synovial membranes and articular surfaces. It manifests primarily as a symmetric, erosive polyarthritis that spares the axial skeleton and is typically associated with the presence in the serum of rheumatoid factor". Other autoimmune joint diseases, drug-induced joint pain, infectious joint pain, degenerative bone and joint diseases, and other datasets that do not meet the definition have all been excluded. These datasets are derived from European descent samples. The RA dataset encompassed 302614 samples (14818 cases and 287796 controls). Furthermore, the Gout dataset included 298684 samples (10888 cases and 287796 controls). The participants' genetic backgrounds in this study were confined to European ancestry, including individuals of both sexes. The original studies of the selected GWAS datasets were approved by the ethics committee, and all the participants in the original research obtained informed consent. The datasets used in this study were publicly accessible, therefore ethical approval was deemed unnecessary. (The detailed GWAS can be found in Table 1)

Selection of Instrumental Variables

To ensure effective IVs, this study strictly adheres to three core assumptions: (1) the correlation hypothesis: selected IVs has a robust correlation with exposure factors; (2) the independence assumption: there's no correlation exists between IVs and any confounders; (3) the exclusion of the restrictive assumption: IVs are exclusively allowed to influence the outcome via exposure factors, without directly affecting on the outcome itself. We adjusted the threshold for $P<5\times10^{-6}$ to obtain adequate exposure-related SNPs. We remove the linkage disequilibrium ($r^2<0.001$,10,000 kb) to reduce the

Table 1 GWAS data sources for instrumental variables selection.

Phenotype	Author or Consortium	Ancestry	Number of SNPs	Sample Size	GWAS ID	Year	Source	Recruitment Strategy
Anti-BK polyomavirus IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006884	2020	GWAS Catalog	Analysis using UKB serological data identified 9724 British adults who provided serum samples. These samples were tested for antibody levels related to over 20 types of microorganisms. Pathogens with a seroprevalence of > 15% were selected. Through GWAS, Human Leukocyte Antigen association studies, and Amino Acid Residue association studies, 13 genetic variants associated with antibody immune responses to 13 infections were ultimately identified, comprising a total of 46 phenotypes.
BK polyomavirus VP1 antibody levels	Butler-Laporte G	European	91,70,146	8555	GCST90006885	2020	GWAS Catalog	
Anti-chlamydia trachomatis IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006886	2020	GWAS Catalog	
Chlamydia trachomatis momp A antibody levels	Butler-Laporte G	European	92,01,352	964	GCST90006887	2020	GWAS Catalog	
Chlamydia trachomatis momp D antibody levels	Butler-Laporte G	European	91,86,659	1371	GCST90006888	2020	GWAS Catalog	
Chlamydia trachomatis pGP3 antibody levels	Butler-Laporte G	European	91,77,921	1784	GCST90006889	2020	GWAS Catalog	
Chlamydia trachomatis PorB antibody levels	Butler-Laporte G	European	91,38,738	273	GCST90006890	2020	GWAS Catalog	
Chlamydia trachomatis tarp-D F1 antibody levels	Butler-Laporte G	European	91,62,340	1635	GCST90006891	2020	GWAS Catalog	
Chlamydia trachomatis tarp-D F2 antibody levels	Butler-Laporte G	European	91,67,334	2074	GCST90006892	2020	GWAS Catalog	
Anti-cytomegalovirus IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006893	2020	GWAS Catalog	
Cytomegalovirus pp28 antibody levels	Butler-Laporte G	European	91,70,765	5087	GCST90006894	2020	GWAS Catalog	
Cytomegalovirus pp52 antibody levels	Butler-Laporte G	European	91,72,314	5681	GCST90006895	2020	GWAS Catalog	
Cytomegalovirus pp150 antibody levels	Butler-Laporte G	European	91,69,705	5136	GCST90006896	2020	GWAS Catalog	
Anti-Epstein-Barr virus IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006897	2020	GWAS Catalog	
Epstein-Barr virus EA-D antibody levels	Butler-Laporte G	European	91,68,986	7763	GCST90006898	2020	GWAS Catalog	
Epstein-Barr virus EBNA-1 antibody levels	Butler-Laporte G	European	91,70,056	7972	GCST90006899	2020	GWAS Catalog	
Epstein-Barr virus VCA p18 antibody levels	Butler-Laporte G	European	91,70,145	8518	GCST90006900	2020	GWAS Catalog	
Epstein-Barr virus ZEBRA antibody levels	Butler-Laporte G	European	91,69,747	8191	GCST90006901	2020	GWAS Catalog	
Anti-human herpes virus 6 IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006902	2020	GWAS Catalog	
Anti-human herpes virus 6 IE1A IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006903	2020	GWAS Catalog	
Human herpes virus 6 IE1A antibody levels	Butler-Laporte G	European	91,70,460	6968	GCST90006904	2020	GWAS Catalog	
Anti-human herpes virus 6 IE1B IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006905	2020	GWAS Catalog	
Human herpesvirus 6 IE1B antibody levels	Butler-Laporte G	European	91,71,247	7119	GCST90006906	2020	GWAS Catalog	

(*Continued*)

Table 1 (Continued).

Phenotype	Author or Consortium	Ancestry	Number of SNPs	Sample Size	GWAS ID	Year	Source	Recruitment Strategy
Human herpes virus 6 p101k antibody levels	Butler-Laporte G	European	91,68,031	1951	GCST90006907	2020	GWAS Catalog	
Anti-human herpes virus 7 IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006908	2020	GWAS Catalog	
Human herpes virus 7 U14 antibody levels	Butler-Laporte G	European	91,71,909	8528	GCST90006909	2020	GWAS Catalog	
Anti-helicobacter pylori IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006910	2020	GWAS Catalog	
Helicobacter pylori CagA antibody levels	Butler-Laporte G	European	91,65,056	985	GCST90006911	2020	GWAS Catalog	
Helicobacter pylori Catalase antibody levels	Butler-Laporte G	European	91,67,570	1558	GCST90006912	2020	GWAS Catalog	
Helicobacter pylori GroEL antibody levels	Butler-Laporte G	European	91,72,299	2716	GCST90006913	2020	GWAS Catalog	
Helicobacter pylori OMP antibody levels	Butler-Laporte G	European	91,67,440	2640	GCST90006914	2020	GWAS Catalog	
Helicobacter pylori UREA antibody levels	Butler-Laporte G	European	91,70,248	2251	GCST90006915	2020	GWAS Catalog	
Helicobacter pylori VacA antibody levels	Butler-Laporte G	European	91,78,635	1571	GCST90006916	2020	GWAS Catalog	
Anti-herpes simplex virus 1 IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006917	2020	GWAS Catalog	
Herpes simplex virus 1 mgG-1 antibody levels	Butler-Laporte G	European	91,70,062	6199	GCST90006918	2020	GWAS Catalog	
Anti-herpes simplex virus 2 IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006919	2020	GWAS Catalog	
Herpes simplex virus 2 mgG-1 antibody levels	Butler-Laporte G	European	91,90,612	1832	GCST90006920	2020	GWAS Catalog	
Anti-polyomavirus 2 IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006921	2020	GWAS Catalog	
Polyomavirus 2 JC VP1 antibody levels	Butler-Laporte G	European	91,71,664	5118	GCST90006922	2020	GWAS Catalog	
Anti-Merkel cell polyomavirus IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006923	2020	GWAS Catalog	
Merkel cell polyomavirus VP1 antibody levels	Butler-Laporte G	European	91,70,966	5915	GCST90006924	2020	GWAS Catalog	
Anti-Toxoplasma gondii IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006925	2020	GWAS Catalog	
Toxoplasma gondii p22 antibody levels	Butler-Laporte G	European	91,77,418	1308	GCST90006926	2020	GWAS Catalog	
Toxoplasma gondii sag1 antibody levels	Butler-Laporte G	European	91,73,429	3919	GCST90006927	2020	GWAS Catalog	
Anti-varicella zoster virus IgG seropositivity	Butler-Laporte G	European	91,70,312	8735	GCST90006928	2020	GWAS Catalog	

(*Continued*)

Table 1 (Continued).

Phenotype	Author or Consortium	Ancestry	Number of SNPs	Sample Size	GWAS ID	Year	Source	Recruitment Strategy
Varicella zoster virus glycoproteins E and I antibody levels	Butler-Laporte G	European	91,72,177	7595	GCST90006929	2020	GWAS Catalog	
Gout	FinnGen	European	2,13,02,819	298684	finngen_R11_M13_GOUT	2023	FinnGen	Chip genotype data processing and QC Samples were genotyped with Illumina and Affymetrix arrays. Genotype calls were made with GenCall and zCall algorithms for Illumina and AxiomGT1 algorithm for Affymetrix data. Furthermore, carrying out quality management and scheduling phase. Genotype imputation was done with the population-specific SISu v4.2 reference panel. The SISu v4.2 reference panel includes five study cohorts: METSIM, FINRISK, Corogene, Biobank of Eastern Finland, and Finnish EUFAM Dyslipidemia Study. Utilize BCOR files for LD estimation.
Rheumatoid arthritis	FinnGen	European	2,13,02,883	302614	finngen_R11_M13_RHEUMA	2023	FinnGen	

superposition effect of the associated SNPs. We utilized Geneatlas (http://geneatlas.roslin.ed.ac.uk/) to search for SNP names and manually screened them to ensure that the selected IVs were not correlated with confounding factors. In addition, to minimize the bias from genotyping techniques, the palindromic SNP was excluded. To evaluate the robustness of IVs, the F-statistics was computed using the formula ($\frac{N-2\times R^2}{1-R^2}$), where N represents the sample size, R^2 represents the proportion of variance in the exposure explained by the SNP.[22] The formula of R^2 incorporates effect allele frequency (EAF), standard error (SE), and effect size (β): $\frac{2\times EAF\times 1-EAF\times \beta^2}{2\times EAF\times 1-EAF\times \beta^2+2\times SE^2\times N\times EAF\times (1-EAF)}$ To prevent bias, weak IVs with an F-statistic less than 10 were filtered out.

MR Analysis

Forward MR Analysis

In the forward analysis, antibody-mediated immune responses served as exposure, with Gout and RA as outcome. IVW provides the most reliable assessment of causality.[23] Consequently, we chose IVW as main analysis method. Additionally, the weighted median, MR-Egger, weighted mode, and simple mode were utilized as secondary supplements and tests. We calculate effect size of β, odds ratio(OR) and 95% confidence intervals(CI) to analyze the association between the antibody-mediated immune responses and both Gout and RA. If the IVW analysis are significant, it indicates the presence of a causal relationship. When two or more analytical methods yield significant results, it indicates that the findings are comparatively stable and reliable.[24] Furthermore, we visualize the effects of the five analytical methods through Scatter plots and Forest plots, and the fitting results intuitively reflect the trend of the impact.

Reverse MR Analysis

In the reverse analysis, same analytical methods were applied, including IVW, weighted median, MR-Egger, weighted mode, and simple mode. Gout and RA were served as exposure while antibody-mediated immune responses considered as outcome. This reverse analysis can also function as validation to exclude potential reverse causality.

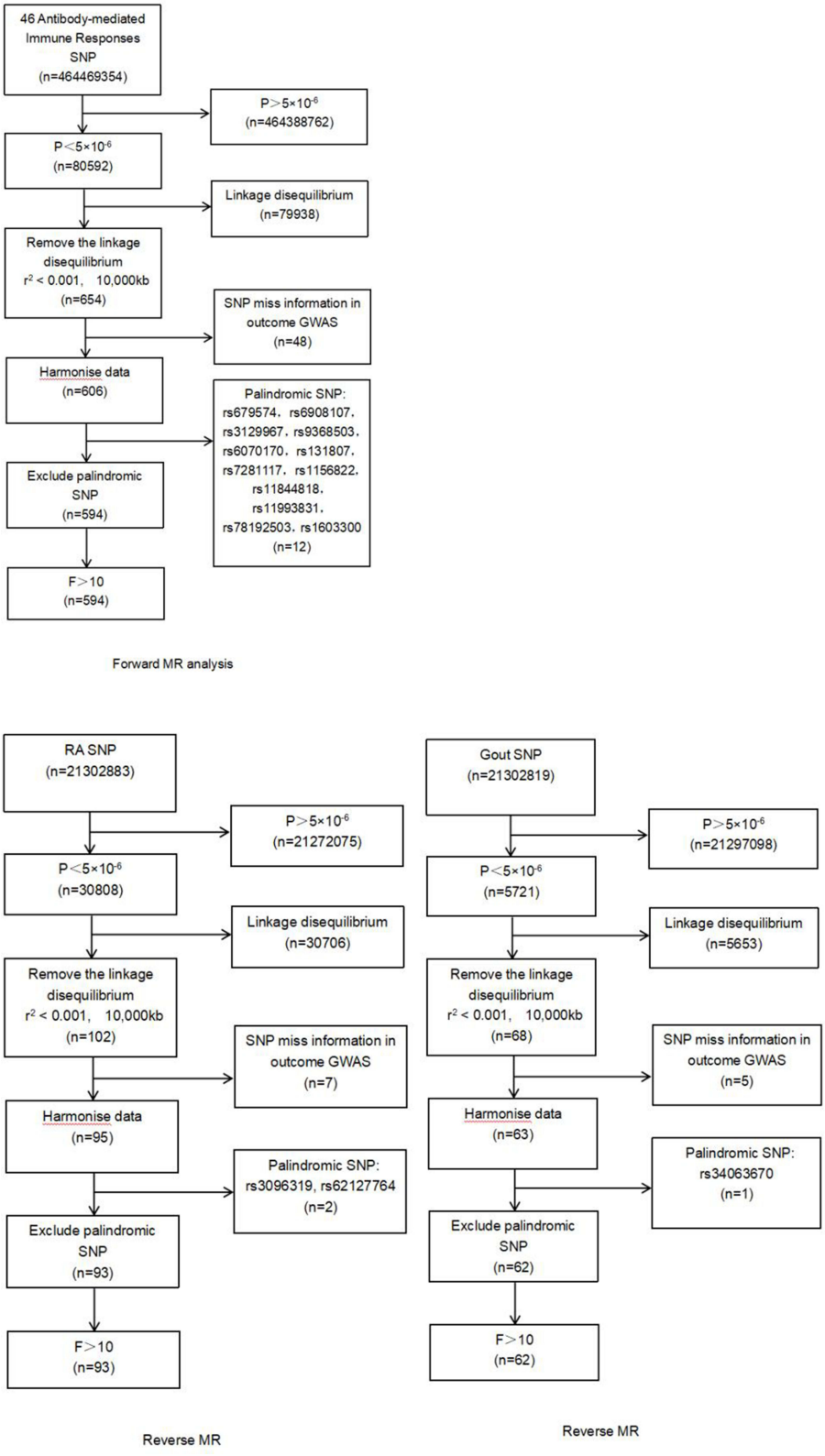

Figure 2 The process of selecting and filtering SNPs.
Abbreviations: RA, Rheumatoid Arthritis; SNPs, single-nucleotide polymorphisms.

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Table 2 MR Results of Causal Effects Between Antibody-Mediated Immune Responses and Gout

GWAS id	Exposure	Outcome	Method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
GCST90006886	Anti-chlamydia trachomatis IgG seropositivity	Gout	MR Egger	11	−0.01624	0.034409	0.648117	−0.08368	0.051198	0.983888	0.919722	1.052531
GCST90006886	Anti-chlamydia trachomatis IgG seropositivity	Gout	Weighted median	11	−0.03973	0.028362	0.161317	−0.09532	0.015864	0.961053	0.909086	1.015991
GCST90006886	Anti-chlamydia trachomatis IgG seropositivity	Gout	Inverse variance weighted	11	−0.04981	0.019907	0.012342	−0.08883	−0.01079	0.951409	0.915002	0.989264
GCST90006886	Anti-chlamydia trachomatis IgG seropositivity	Gout	Simple mode	11	−0.03997	0.041261	0.355482	−0.12085	0.040897	0.960814	0.88617	1.041745
GCST90006886	Anti-chlamydia trachomatis IgG seropositivity	Gout	Weighted mode	11	−0.03731	0.030214	0.245085	−0.09653	0.021907	0.963375	0.90798	1.022149
GCST90006905	Anti-human herpes virus 6 IE1B IgG seropositivity	Gout	MR Egger	11	0.040822	0.053629	0.466016	−0.06429	0.145936	1.041667	0.937732	1.157122
GCST90006905	Anti-human herpes virus 6 IE1B IgG seropositivity	Gout	Weighted median	11	−0.07928	0.032831	0.01575	−0.14362	−0.01493	0.923785	0.866213	0.985184
GCST90006905	Anti-human herpes virus 6 IE1B IgG seropositivity	Gout	Inverse variance weighted	11	−0.06148	0.025334	0.015228	−0.11114	−0.01183	0.94037	0.894817	0.988241
GCST90006905	Anti-human herpes virus 6 IE1B IgG seropositivity	Gout	Simple mode	11	−0.08468	0.054544	0.151603	−0.19158	0.022229	0.91881	0.825652	1.022478
GCST90006905	Anti-human herpes virus 6 IE1B IgG seropositivity	Gout	Weighted mode	11	−0.08645	0.052234	0.128902	−0.18883	0.015925	0.917179	0.827927	1.016053
GCST90006913	Helicobacter pylori GroEL antibody levels	Gout	MR Egger	7	−0.09943	0.101489	0.37224	−0.29834	0.099492	0.905357	0.742046	1.10461
GCST90006913	Helicobacter pylori GroEL antibody levels	Gout	Weighted median	7	−0.09084	0.054303	0.09436	−0.19727	0.015594	0.913164	0.820966	1.015716
GCST90006913	Helicobacter pylori GroEL antibody levels	Gout	Inverse variance weighted	7	−0.08748	0.043601	0.044813	−0.17294	−0.00202	0.916237	0.84119	0.997979
GCST90006913	Helicobacter pylori GroEL antibody levels	Gout	Simple mode	7	−0.03752	0.08164	0.662023	−0.19753	0.122498	0.963178	0.820754	1.130316
GCST90006913	Helicobacter pylori GroEL antibody levels	Gout	Weighted mode	7	−0.13504	0.078606	0.136613	−0.28911	0.019027	0.873681	0.748932	1.01921
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	Gout	MR Egger	16	0.116292	0.082695	0.181449	−0.04579	0.278373	1.123323	0.955242	1.320979
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	Gout	Weighted median	16	0.139209	0.054492	0.010628	0.032406	0.246013	1.149365	1.032936	1.278916
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	Gout	Inverse variance weighted	16	0.11523	0.040592	0.004529	0.035669	0.194791	1.122131	1.036313	1.215057
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	Gout	Simple mode	16	0.153619	0.098245	0.138751	−0.03894	0.346179	1.166047	0.961808	1.413656
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	Gout	Weighted mode	16	0.165954	0.091655	0.09027	−0.01369	0.345597	1.180519	0.986404	1.412833

Sensitivity Analysis

After analyzing the results, we ascertain the reliability of the findings by conducting sensitivity analysis. Initially, we quantified the heterogeneity of genetic variations using the Cochran Q test, where P>0.05 states that heterogeneity was not significantly detected. Subsequently, we employed MR-egger intercept analysis to estimate horizontal pleiotropy. The P> 0.05 indicates that pleiotropy was not detected, and the results were reliable. Additionally, we used MR-PRESSO to further investigate pleiotropy. The MR-Egger can also be applied to analyze the heterogeneity among genetic variants. Finally, we used the Leave-one-out method to assess whether any single SNP significantly impacts the results, thereby verifying the reliability of the results.

Results

Select Instrumental Variables

SNP linked to antibody-mediated immune responses, Gout, and RA were identified as IVs. First, we pinpointed 654 SNPs associated with 46 antibody-mediated immune responses (refer to Supplementary Table 1). Then we identified 68 SNPs correlated with Gout and 102 SNPs related with RA (refer to Supplementary Table 2). The F statistics for all instrumental variables surpassed 10 (ranging from 20.740 to 216.331). (The process of selecting and filtering SNPs can be found in Figure 2).

The Causal Relationship Between Antibody-Mediated Immune Responses and Gout, RA

OR<1 indicates that exposure may reduce the risk of the outcome occurring. In forward MR, it represents a negative correlation between antibody-mediated immune responses and the occurrence of Gout or RA, meaning it would decrease the incidence of Gout or RA. In reverse MR, it indicates a negative correlation between Gout or RA and antibody-mediated immune responses, which would lower the levels of corresponding antibodies. OR>1 suggests that exposure may increase the risk of the outcome occurring. In forward MR, it signifies a positive correlation between antibody-mediated immune responses and the occurrence of Gout or RA, meaning it would increase the likelihood of Gout or RA.

exposure	outcome	method	or(95%CI)	pval
Anti−chlamydia trachomatis IgG seropositivity	Gout	MR Egger	0.984(0.920, 1.053)	6.48e−01
Anti−chlamydia trachomatis IgG seropositivity	Gout	Weighted median	0.961(0.909, 1.016)	1.61e−01
Anti−chlamydia trachomatis IgG seropositivity	Gout	Inverse variance weighted	0.951(0.915, 0.989)	1.23e−02
Anti−chlamydia trachomatis IgG seropositivity	Gout	Simple mode	0.961(0.886, 1.042)	3.55e−01
Anti−chlamydia trachomatis IgG seropositivity	Gout	Weighted mode	0.963(0.908, 1.022)	2.45e−01
Anti−human herpes virus 6 IE1B IgG seropositivity	Gout	MR Egger	1.042(0.938, 1.157)	4.66e−01
Anti−human herpes virus 6 IE1B IgG seropositivity	Gout	Weighted median	0.924(0.866, 0.985)	1.58e−02
Anti−human herpes virus 6 IE1B IgG seropositivity	Gout	Inverse variance weighted	0.940(0.895, 0.988)	1.52e−02
Anti−human herpes virus 6 IE1B IgG seropositivity	Gout	Simple mode	0.919(0.826, 1.022)	1.52e−01
Anti−human herpes virus 6 IE1B IgG seropositivity	Gout	Weighted mode	0.917(0.828, 1.016)	1.29e−01
Helicobacter pylori GroEL antibody levels	Gout	MR Egger	0.905(0.742, 1.105)	3.72e−01
Helicobacter pylori GroEL antibody levels	Gout	Weighted median	0.913(0.821, 1.016)	9.44e−02
Helicobacter pylori GroEL antibody levels	Gout	Inverse variance weighted	0.916(0.841, 0.998)	4.48e−02
Helicobacter pylori GroEL antibody levels	Gout	Simple mode	0.963(0.821, 1.130)	6.62e−01
Helicobacter pylori GroEL antibody levels	Gout	Weighted mode	0.874(0.749, 1.019)	1.37e−01
Polyomavirus 2 JC VP1 antibody levels	Gout	MR Egger	1.123(0.955, 1.321)	1.81e−01
Polyomavirus 2 JC VP1 antibody levels	Gout	Weighted median	1.149(1.033, 1.279)	1.06e−02
Polyomavirus 2 JC VP1 antibody levels	Gout	Inverse variance weighted	1.122(1.036, 1.215)	4.53e−03
Polyomavirus 2 JC VP1 antibody levels	Gout	Simple mode	1.166(0.962, 1.414)	1.39e−01
Polyomavirus 2 JC VP1 antibody levels	Gout	Weighted mode	1.181(0.986, 1.413)	9.03e−02

Figure 3 Forest plot visualization of the causal effect of antibody-mediated immune responses on Gout.
Abbreviations: or, odds ratio; CI, confidence interval.

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In reverse MR, it represents a positive correlation between Gout or RA and antibody-mediated immune responses, which would raise the levels of corresponding antibodies.

As depicted in Table 2 and Figure 3, the IVW analysis reveal Anti-chlamydia trachomatis IgG seropositivity (OR=0.951, 95% CI =0.915–0.989, P=0.012), Anti-human herpes virus 6 IE1B IgG seropositivity (OR=0.940, 95% CI =0.895–0.988, P=0.015), Helicobacter pylori GroEL antibody levels (OR=0.916, 95% CI =0.841–0.998, P=0.045) were inversely associated with Gout, representing that these antibody-mediated immune responses are protective factors for Gout in certain genetic circumstances, potentially decreasing the likelihood of Gout attacks. While Polyomavirus 2 JC VP1 antibody levels (OR = 1.122, 95% CI =1.036–1.215, P=0.005) exhibited a positive correlation with Gout, indicating that the

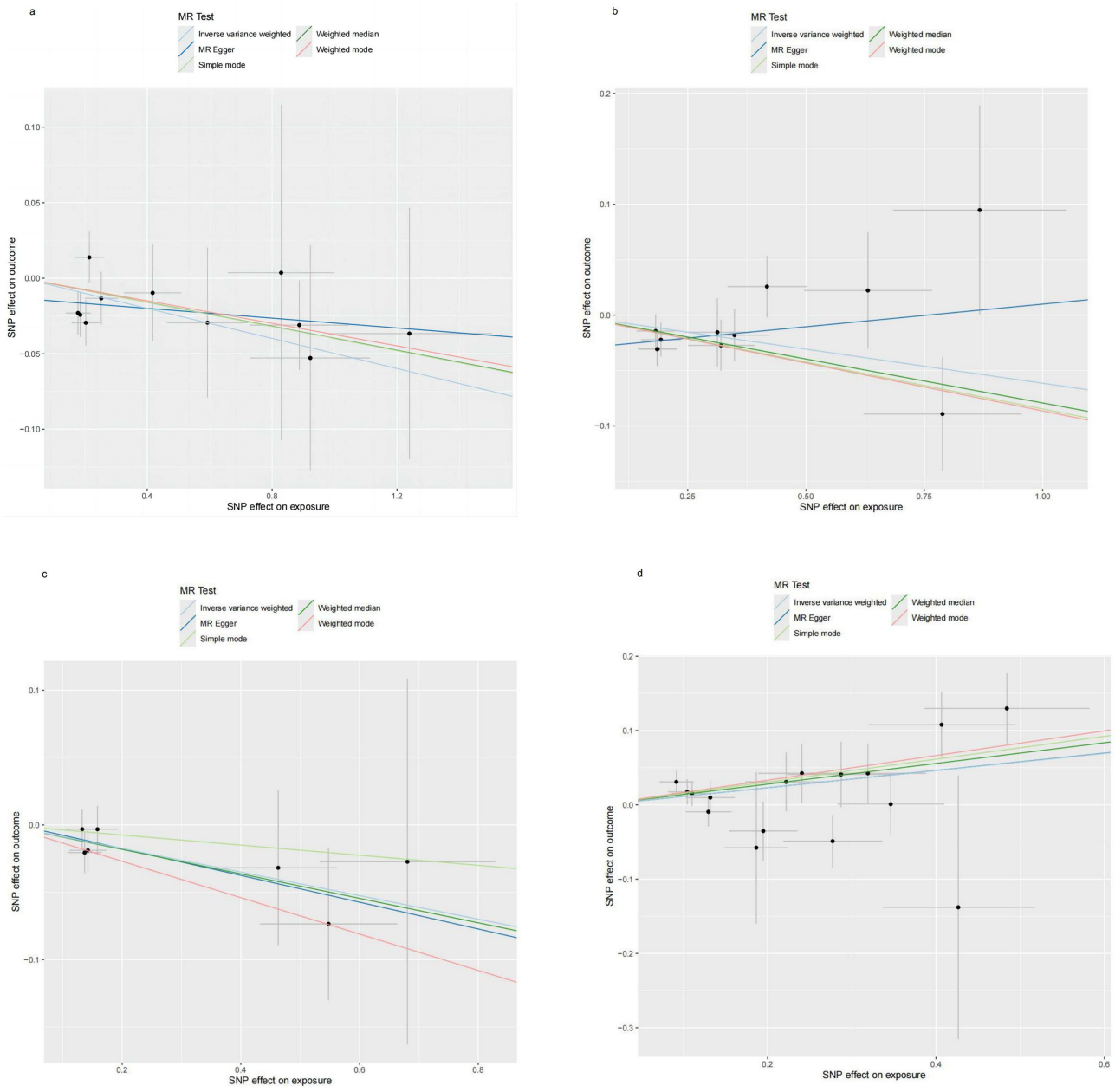

Figure 4 Scatter plots for the effect of antibody-mediated immune responses on Gout. (**a**) Analysis for "Anti-chlamydia trachomatis IgG seropositivity" on "Gout". (**b**) Analysis for "Anti-human herpes virus 6 IE1B IgG seropositivity" on "Gout". (**c**) Analysis for "Helicobacter pylori GroEL antibody levels" on "Gout". (**d**) Analysis for "Polyomavirus 2 JC VP1 antibody levels" on "Gout".
Abbreviations: SNP, single-nucleotide polymorphism.

immune response mediated by this antibody is a risk factor for Gout attacks (refer to Figures 4 and 5). No significant heterogeneity or horizontal pleiotropy (both P> 0.05) were found in subsequent sensitivity tests (refer to Table 3), and the Leave-one-out revealed that the results were relatively stable, implying their reliability (refer to Figure 6). After the analysis of IVW and Weighted median, Anti-human herpes virus 6 IE1B IgG seropositivity showed a more stable negative causality with Gout, whereas Polyomavirus 2 JC VP1 antibody levels represent a more stable positive causality.

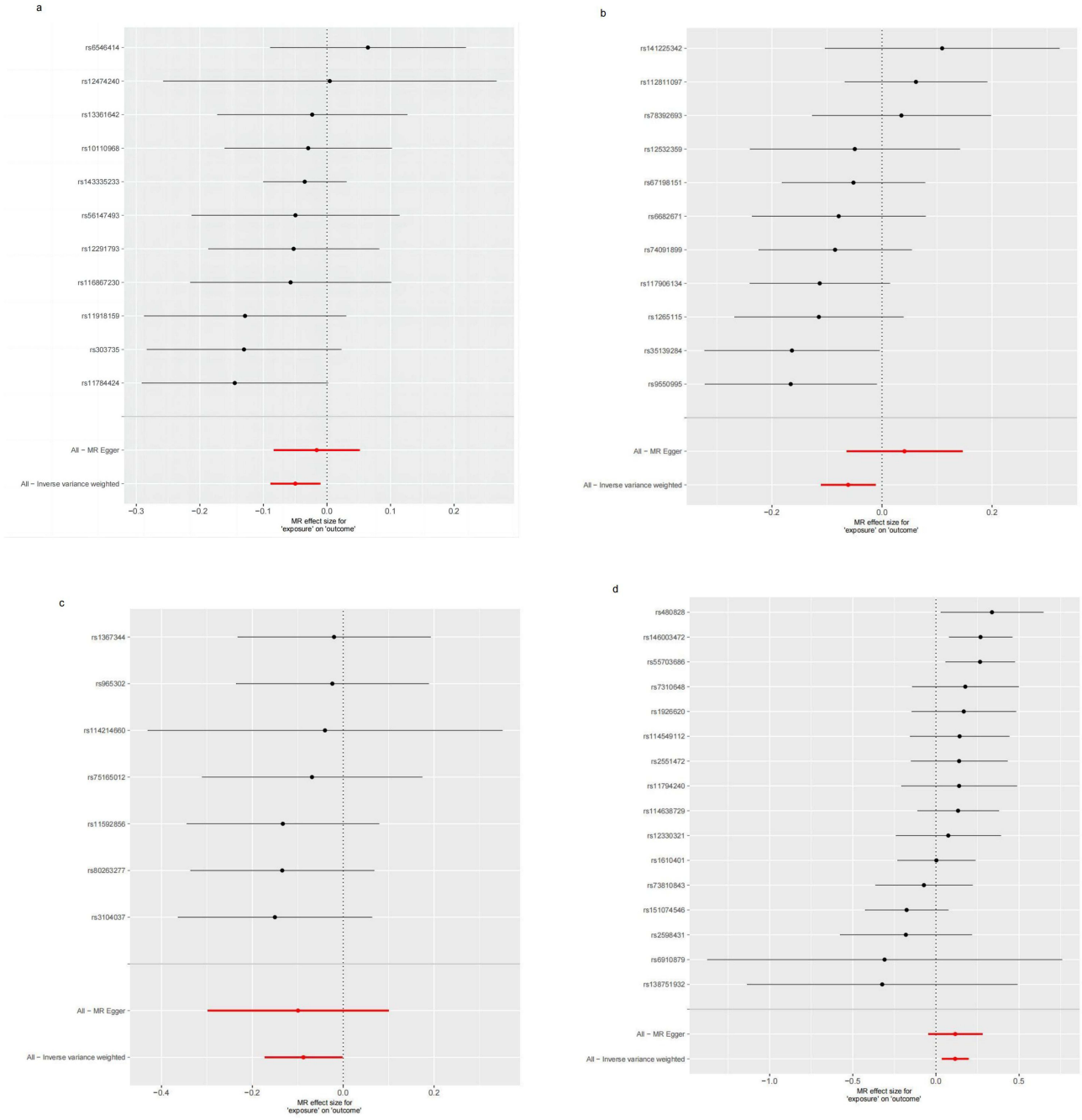

Figure 5 Forest plots for the effect of antibody-mediated immune responses on Gout. (**a**) Analysis for "Anti-chlamydia trachomatis IgG seropositivity" on "Gout". (**b**) Analysis for "Anti-human herpes virus 6 IE1B IgG seropositivity" on "Gout". (**c**) Analysis for "Helicobacter pylori GroEL antibody levels" on "Gout". (**d**) Analysis for "Polyomavirus 2 JC VP1 antibody levels" on "Gout".
Abbreviations: SNP, single-nucleotide polymorphism.

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Table 3 Mendelian Randomization Sensitivity Analysis of Antibody-Mediated Immune Responses

GWAS id	Exposure	Outcome	Pleiotropy Test				Heterogeneity Test		
			MR Egger			MR-PRESSO	Method	Cochran's Q statistic	*P*-value
			Intercept	SE	*P*-value				
GCST90006886	Anti-chlamydia trachomatis IgG seropositivity	Gout	−0.01342	0.01122	0.262231	0.8223333	MR Egger	4.931620861	0.84022782
							Inverse variance weighted	6.362190383	0.783971299
GCST90006905	Anti-human herpes virus 6 IE1B IgG seropositivity	Gout	−0.0309	0.014605	0.063472	0.3283333	MR Egger	7.451099101	0.59026109
							Inverse variance weighted	11.92759844	0.289931304
GCST90006913	Helicobacter pylori GroEL antibody levels	Gout	0.00228	0.017493	0.901381	0.96	MR Egger	1.511841649	0.911699259
							Inverse variance weighted	1.528829355	0.957556574
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	Gout	−0.00022	0.015019	0.988319	0.246	MR Egger	18.49244896	0.185263481
							Inverse variance weighted	18.49274239	0.23764683
GCST90006885	BK polyomavirus VP1 antibody levels	RA	0.018008	0.01253	0.193815	0.2686667	MR Egger	8.094914848	0.324298909
							Inverse variance weighted	10.48356199	0.23271173
GCST90006901	Epstein-Barr virus ZEBRA antibody levels	RA	−0.01786	0.019365	0.374456	<0.000333333333333333	MR Egger	50.54468573	1.12E-06
							Inverse variance weighted	54.12898501	5.74E-07
GCST90006912	Helicobacter pylori Catalase antibody levels	RA	−0.0145	0.01084	0.222873	0.3913333	MR Egger	6.497405315	0.48301146
							Inverse variance weighted	8.286385021	0.406006997
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	RA	−0.13406	0.060639	0.044199	<0.000333333333333333	MR Egger	441.164679	2.62E-85
							Inverse variance weighted	595.1781944	3.76E-117

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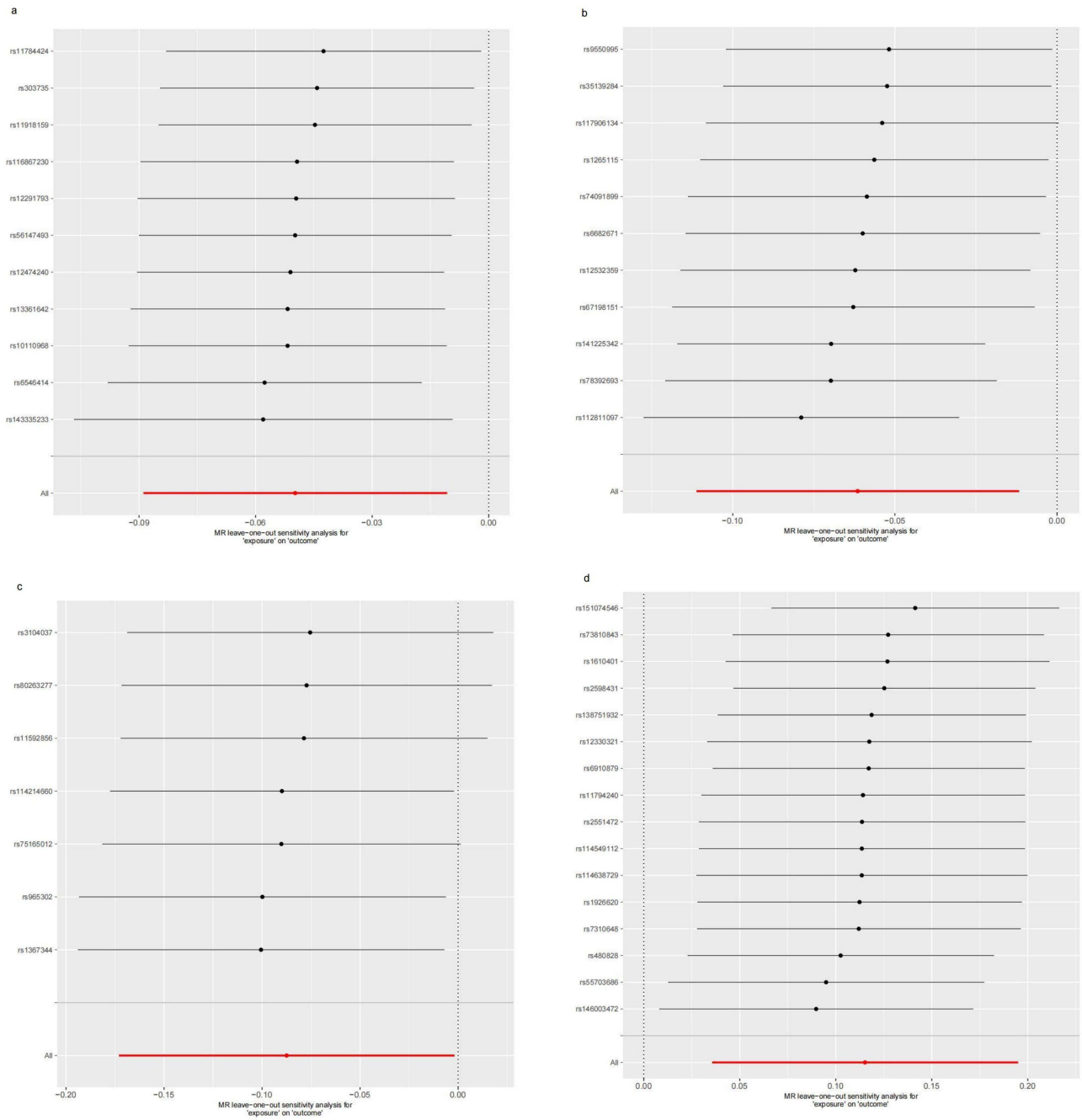

Figure 6 Leave-one-out sensitivity analysis for antibody-mediated immune responses on Gout. (**a**) Analysis for "Anti-chlamydia trachomatis IgG seropositivity" on "Gout". (**b**) Analysis for "Anti-human herpes virus 6 IE1B IgG seropositivity" on "Gout". (**c**) Analysis for "Helicobacter pylori GroEL antibody levels" on "Gout". (**d**) Analysis for "Polyomavirus 2 JC VP1 antibody levels" on "Gout".
Abbreviations: MR, Mendelian randomization.

As pictured in Figure 7, the IVW analysis revealed that BK polyomavirus VP1 antibody levels (OR = 0.825, 95% CI =0.727–0.937, P=0.003), Epstein-Barr virus ZEBRA antibody levels (OR=0.859, 95% CI =0.756–0.976, P=0.020), Helicobacter pylori Catalase antibody levels (OR=0.957, 95% CI =0.919–0.996, P=0.029) were inversely correlated with RA. This suggests that these antibody-mediated immune responses are important protective factors in RA. Conversely, Polyomavirus 2 JC VP1 antibody levels (OR=1.484, 95% CI =1.025–2.148, P=0.037) was positively associated with RA, implying the hazards for RA (refer to Table 4, Figures 8 and 9). In the sensitivity test, heterogeneity

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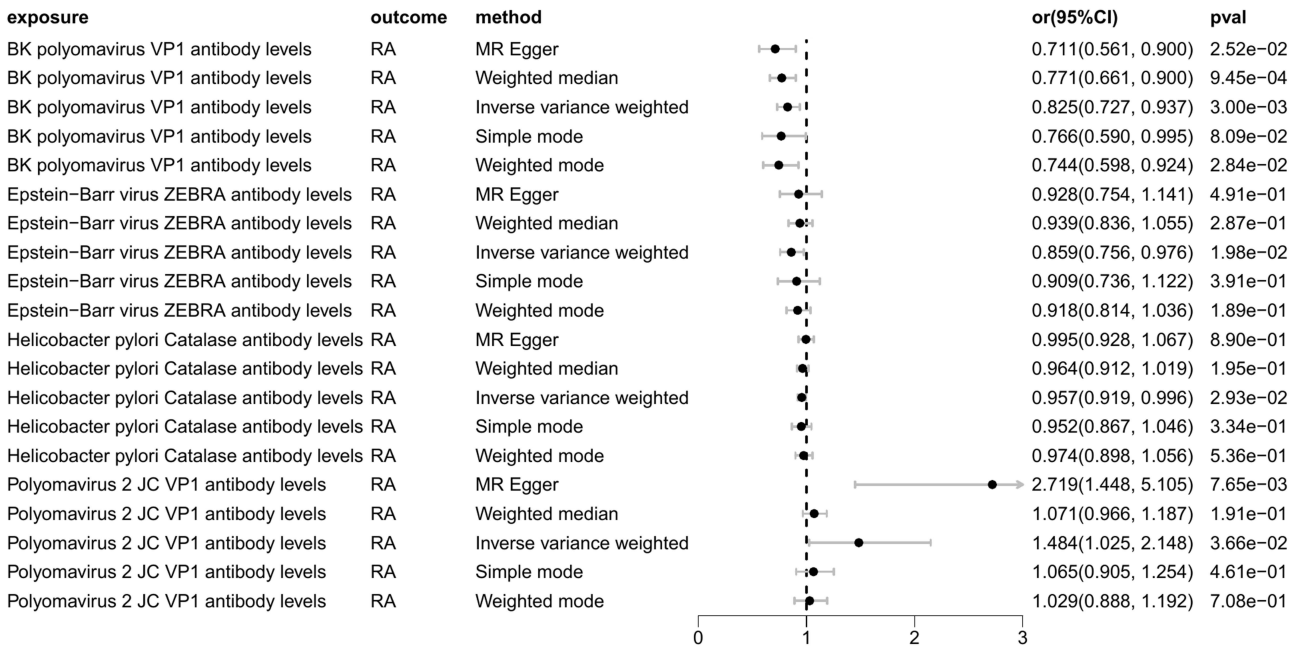

Figure 7 Forest plot visualization of the causal effect of antibody-mediated immune responses on RA.
Abbreviations: or, odds ratio; CI, confidence interval; RA, Rheumatoid Arthritis.

was observed in the results of Epstein-Barr virus ZEBRA antibody levels and Polyomavirus 2 JC VP1 antibody levels (P <0.05). The global test of MR-PRESSO revealed pleiotropy.(P <0.05). The remaining results did not exhibit significant heterogeneity or horizontal pleiotropy (both P> 0.05) (refer to Table 3). After employing the Leaf-one-out method, no single SNP substantially alter the results, indicating that the results were relatively stable (refer to Figure 10). The analysis of IVW, weighted median, weighted mode and MR-Egger revealed that the positive causality of BK polyomavirus VP1 antibody levels on RA is more stable.

The Causal Relationship Between Gout, RA and Antibody-Mediated Immune Responses

The IVW analysis indicates that Gout is causally associated with four antibody-mediated immune responses, while RA is causally linked with five antibody-mediated immune responses. As illustrated in Figure 11, Gout positively correlates with BK polyomavirus VP1 antibody levels (OR = 1.057, 95% CI =1.007–1.109, P=0.025), Chlamydia trachomatis tarp-D F2 antibody levels (OR=1.113, 95% CI =1.006–1.231, P=0.038), Varicella zoster virus glycoproteins E and I antibody levels (OR=1.061, 95% CI =1.009–1.117, P=0.022). This suggests that the onset of Gout, influenced by genetic variants, will bolster the relevant antibody-mediated immune responses. A negative correlation with Human herpes virus 6 p101k antibody levels (OR = 0.897, 95% CI =0.811–0.993, P=0.037) was also observed, suggesting that Gout attenuates the antibody-mediated immune response (refer to Table 5, Figures 12 and 13). No significant heterogeneity or pleiotropy (P> 0.05) was found (refer to Table 6). Upon assessing the sensitivity of Gout to Human herpes virus 6 p101k antibody levels' causal relationship by using Leave-one-out method, a SNP (rs117581227) was identified, and its removal resulted a substantial alteration of the result (P_{IVW}=0.161). This indicates that the result may be unstable yet the remaining causality was considered reliable through Leave-one-out analysis (refer to Figure 14). After the analysis of IVW, weighted median and MR Egger, Gout exhibited greater stability in its association with BK polyomavirus VP1 antibody levels and Chlamydia trachomatis tarp-D F2 antibody levels.

As shown in Figure 15, RA will increase the Chlamydia trachomatis pGP3 antibody levels (OR = 1.109, 95% CI =1.008–1.221, P=0.034), Anti-human herpes virus 6 IE1A IgG seropositivity (OR=1.165, 95% CI =1.021–1.329,

Table 4 MR Results of Causal Effects Between Antibody-Mediated Immune Responses and RA

GWAS id	Exposure	Outcome	Method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
GCST90006885	BK polyomavirus VP1 antibody levels	RA	MR Egger	9	−0.34142	0.120457	0.025248	−0.57751	−0.10532	0.710764	0.561294	0.900036
GCST90006885	BK polyomavirus VP1 antibody levels	RA	Weighted median	9	−0.25964	0.078524	0.000945	−0.41354	−0.10573	0.771332	0.661302	0.899668
GCST90006885	BK polyomavirus VP1 antibody levels	RA	Inverse variance weighted	9	−0.19192	0.064667	0.002999	−0.31867	−0.06518	0.825371	0.727117	0.936903
GCST90006885	BK polyomavirus VP1 antibody levels	RA	Simple mode	9	−0.26645	0.133412	0.080869	−0.52794	−0.00496	0.766095	0.589821	0.995052
GCST90006885	BK polyomavirus VP1 antibody levels	RA	Weighted mode	9	−0.29605	0.110951	0.028437	−0.51351	−0.07859	0.743751	0.59839	0.924423
GCST90006901	Epstein-Barr virus ZEBRA antibody levels	RA	MR Egger	14	−0.07509	0.105693	0.491019	−0.28224	0.132071	0.927663	0.75409	1.14119
GCST90006901	Epstein-Barr virus ZEBRA antibody levels	RA	Weighted median	14	−0.06323	0.059357	0.286784	−0.17957	0.053112	0.938731	0.835633	1.054548
GCST90006901	Epstein-Barr virus ZEBRA antibody levels	RA	Inverse variance weighted	14	−0.15163	0.065097	0.019847	−0.27922	−0.02404	0.85931	0.756377	0.976251
GCST90006901	Epstein-Barr virus ZEBRA antibody levels	RA	Simple mode	14	−0.0957	0.107777	0.390698	−0.30694	0.115541	0.908736	0.735692	1.122481
GCST90006901	Epstein-Barr virus ZEBRA antibody levels	RA	Weighted mode	14	−0.08541	0.061661	0.189296	−0.20627	0.035442	0.918132	0.813614	1.036077
GCST90006912	Helicobacter pylori Catalase antibody levels	RA	MR Egger	9	−0.0051	0.035544	0.889901	−0.07477	0.064563	0.994911	0.927959	1.066693
GCST90006912	Helicobacter pylori Catalase antibody levels	RA	Weighted median	9	−0.03675	0.028361	0.195061	−0.09234	0.018839	0.963918	0.911798	1.019017
GCST90006912	Helicobacter pylori Catalase antibody levels	RA	Inverse variance weighted	9	−0.04439	0.020364	0.029251	−0.08431	−0.00448	0.956576	0.919148	0.995528
GCST90006912	Helicobacter pylori Catalase antibody levels	RA	Simple mode	9	−0.04922	0.047897	0.334178	−0.1431	0.044656	0.951971	0.866669	1.045668
GCST90006912	Helicobacter pylori Catalase antibody levels	RA	Weighted mode	9	−0.0267	0.041323	0.536336	−0.10769	0.054297	0.973656	0.897905	1.055798
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	RA	MR Egger	16	1.000195	0.321441	0.007654	0.37017	1.63022	2.718812	1.447981	5.104997
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	RA	Weighted median	16	0.068643	0.052549	0.191459	−0.03435	0.171639	1.071054	0.966231	1.18725
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	RA	Inverse variance weighted	16	0.394677	0.188791	0.036569	0.024646	0.764708	1.483905	1.024953	2.148367
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	RA	Simple mode	16	0.063123	0.083373	0.460713	−0.10029	0.226535	1.065158	0.904576	1.254246
GCST90006922	Polyomavirus 2 JC VP1 antibody levels	RA	Weighted mode	16	0.028661	0.075187	0.708402	−0.11871	0.176029	1.029076	0.888069	1.192472

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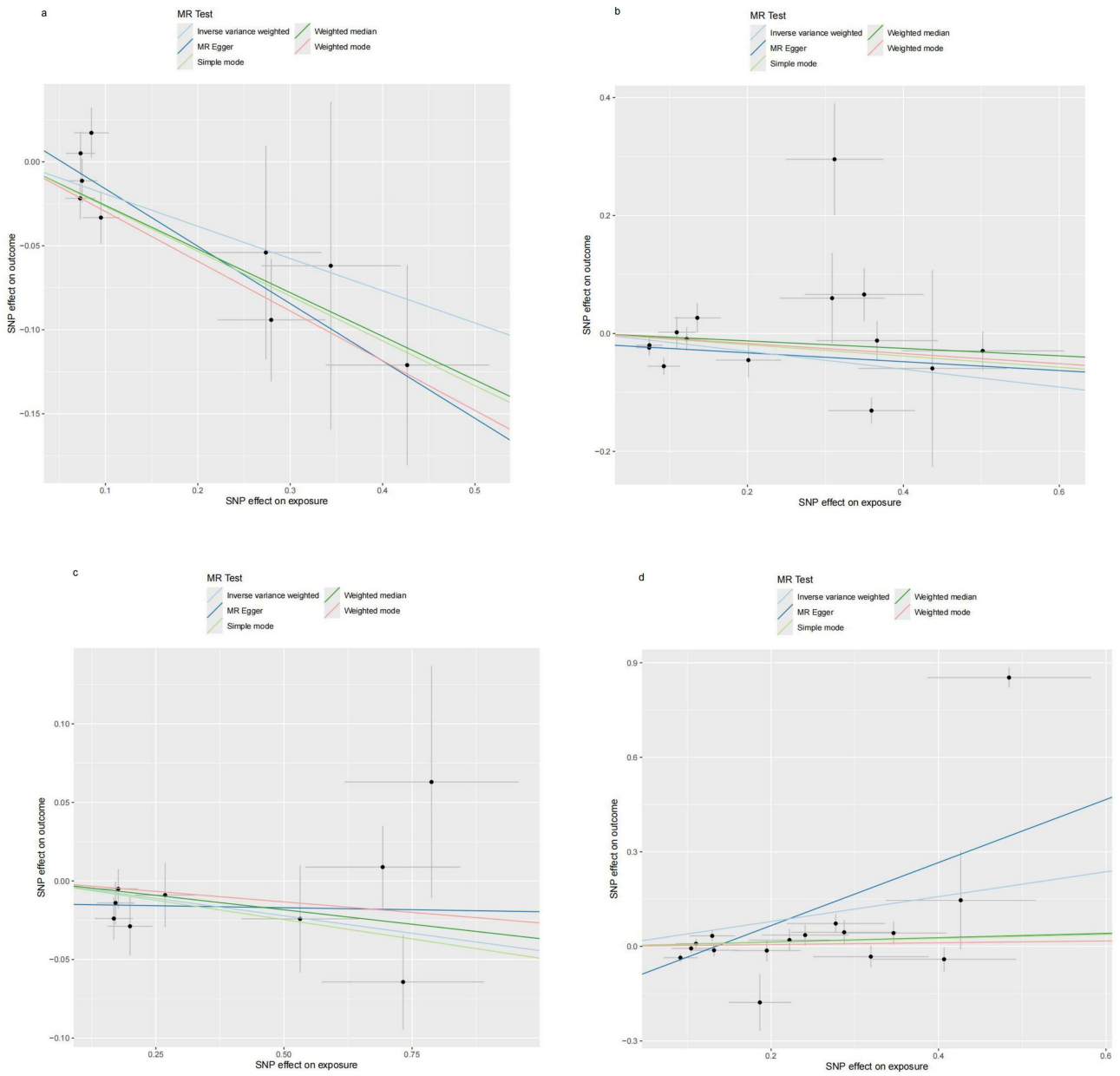

Figure 8 Scatter plots for the effect of antibody-mediated immune responses on RA. (**a**) Analysis for "BK polyomavirus VP1 antibody levels" on "RA". (**b**) Analysis for "Epstein-Barr virus ZEBRA antibody levels" on "RA". (**c**) Analysis for "Helicobacter pylori Catalase antibody levels" on "RA". (**d**) Analysis for "Polyomavirus 2 JC VP1 antibody levels" on "RA".

Abbreviations: SNP, single-nucleotide polymorphism; RA, Rheumatoid Arthritis.

P=0.023), Human herpes virus 6 IE1A antibody levels (OR=1.063, 95% CI =1.000–1.131, P=0.048), Anti-human herpes virus 7 IgG seropositivity (OR=1.271, 95% CI =1.035–1.561, P=0.022), Merkel cell polyomavirus VP1 antibody levels (OR=1.093, 95% CI =1.032–1.158, P=0.002). Importantly, no negative causal relationship was found between RA and other immune responses (refer to Table 7, Figures 16 and 17). Further sensitivity analysis reveals that Anti-human herpes virus 6 IE1A IgG seropositivity and Human herpes virus 6 IE1A antibody levels exhibit heterogeneous and pleiotropy (P <0.05) (refer to Table 6). The Leave-one-out analysis indicates a SNP (rs189189451) that modifies the causal relationship between RA and Chlamydia trachomatis pGP3 antibody levels upon its elimination (P_{IVW}=0.224), indicating the

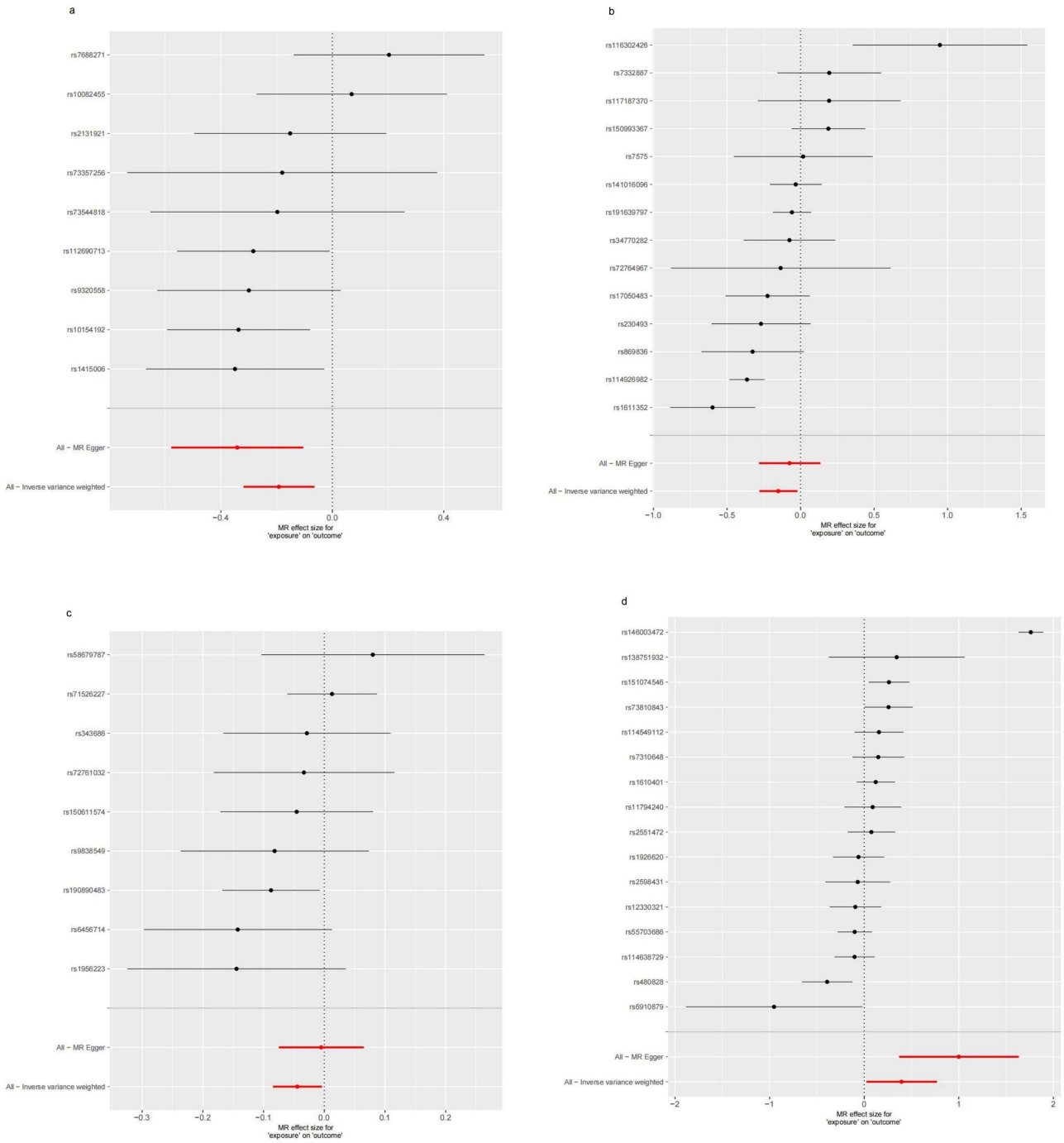

Figure 9 Forest plots for the effect of antibody-mediated immune responses on RA. (**a**) Analysis for "BK polyomavirus VP1 antibody levels" on "RA". (**b**) Analysis for "Epstein-Barr virus ZEBRA antibody levels" on "RA". (**c**) Analysis for "Helicobacter pylori Catalase antibody levels" on "RA". (**d**) Analysis for "Polyomavirus 2 JC VP1 antibody levels" on "RA".

Abbreviations: SNP, single-nucleotide polymorphism; RA, Rheumatoid Arthritis.

instability of this analysis. The remaining results appeared relatively stable (refer to Figure 18). The analysis of IVW, MR-Egger, weighted median confirms that the positive causal relationship between RA and Merkel cell polyomavirus VP1 antibody levels is more robust.

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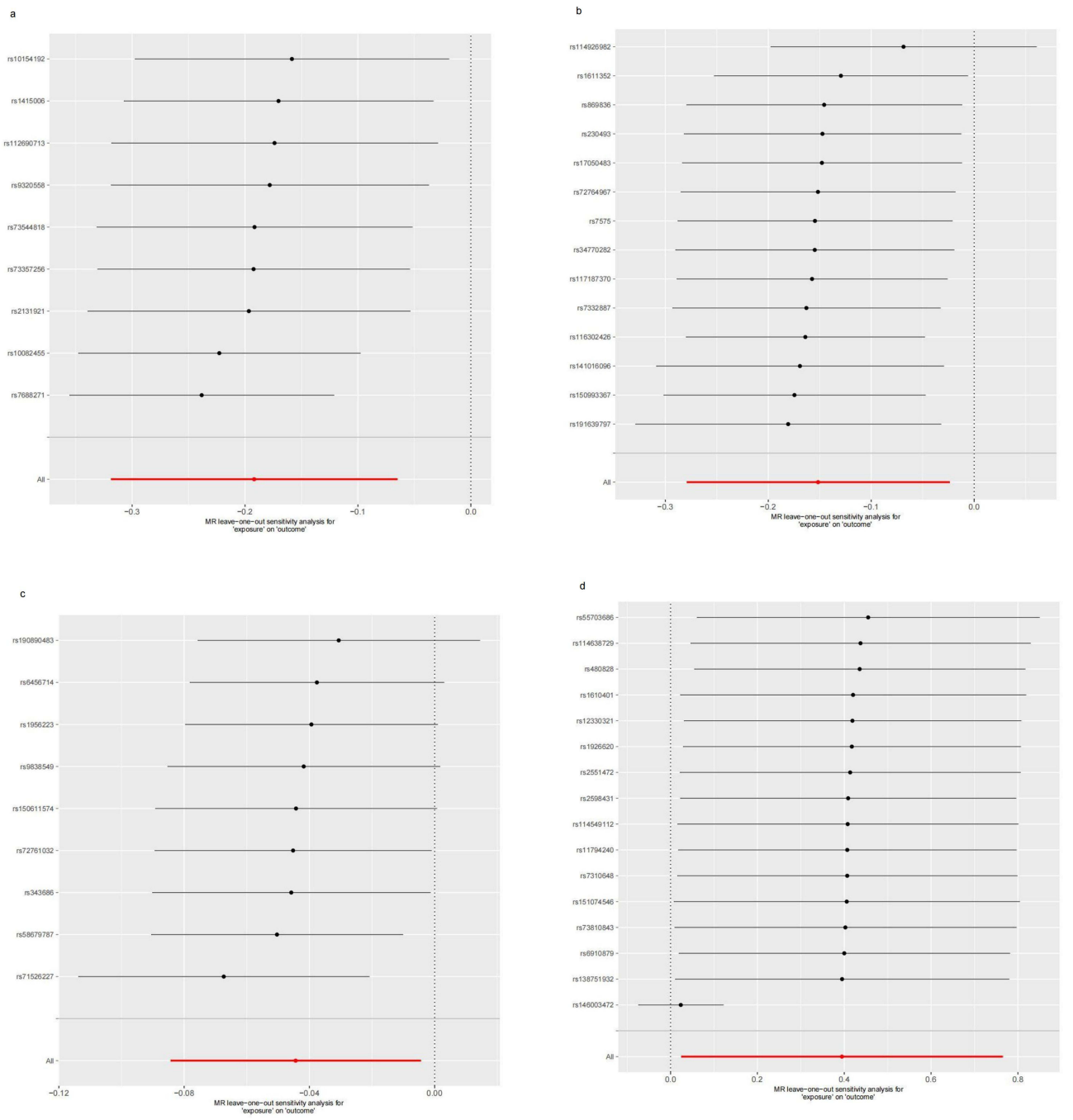

Figure 10 Leave-one-out sensitivity analysis for antibody-mediated immune responses on RA. (**a**) Analysis for "BK polyomavirus VP1 antibody levels" on "RA". (**b**) Analysis for "Epstein-Barr virus ZEBRA antibody levels" on "RA". (**c**) Analysis for "Helicobacter pylori Catalase antibody levels" on "RA". (**d**) Analysis for "Polyomavirus 2 JC VP1 antibody levels" on "RA".
Abbreviation: MR, Mendelian randomization.

Discussion

In this research, we used the most extensive infectious disease-related GWAS data for a bidirectional two-sample MR to evaluate the interaction relationship with non-infectious inflammatory joint diseases. In particular, we identified four antibody-mediated immune responses that could potentially play a causative role in Gout, and two antibody-mediated immune responses that may potentially cause RA. We focus on some stable and significant analytical results, among

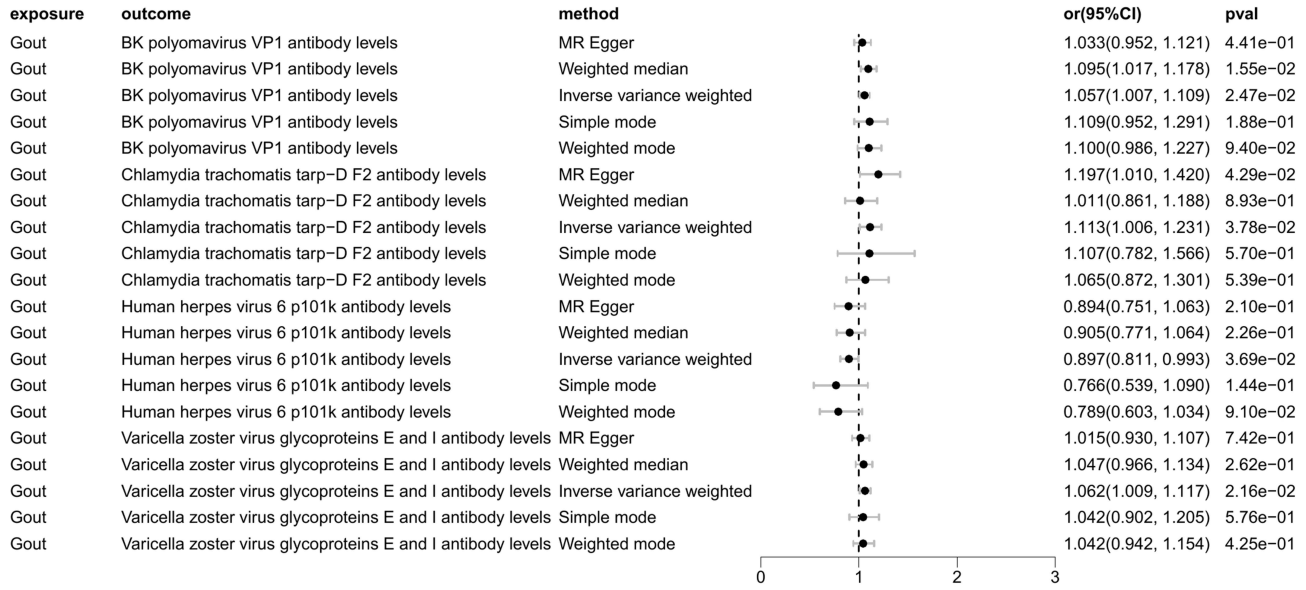

Figure 11 Forest plot visualization of the causal effect of Gout on antibody-mediated immune responses.
Abbreviations: or, odds ratio; CI, confidence interval.

which the more significant analysis suggest that Anti-human herpes virus 6 IE1B IgG seropositivity appears to serve as a protective factor against Gout, while Polyomavirus 2 JC VP1 antibody levels pose a risk for Gout, higher BK polyomavirus VP1 antibody levels have been identified as a protective factor for RA. In the reverse MR analysis, we also discovered that Gout has a significant positive causality with BK polyomavirus VP1 antibody levels, as well as Chlamydia trachomatis tarp-D F2 antibody levels. Furthermore, we observed that RA has a positive correlation with Merkel cell polyomavirus VP1 antibody levels. Although the correlation between antibody levels and disease outcomes remains to be exactly elaborated, existing studies provide a theoretical basis for the correlation.

Human herpes virus 6 (HHV-6) is a virus associated with roseola rash in infants. More than 90% individuals infected with HHV-6B are under the age of three and enter the latent phase following primary infection, resulting in lifelong latent infection.[25,26] The study found that B cells can induce the transformation of effector T cells, leading to an increase in the activation of Treg cell populations and a decrease in Th1 and Th17 cells.[27–29] Existing studies have shown that HHV-6 can trigger specific Treg cells to inhibit immune responses, which may serve as a mechanism for immune evasion. Viral-specific Treg cells can directly inhibit effector T cell and impair the function of dendritic cells (DCs), thereby affecting both innate and adaptive immunity.[30] Treg cells can secrete high levels of IL-10 and TGF-β to participate in the suppression of inflammation and immunity, driving the transformation of T cells into Treg cells.[31,32] MUS induced changes in the Th 17/Treg ratio expressed in Gout model mice are similar to the process of Gout's onset.[33] Wang et al also discovered that Treg cells inhibited the progression of Gout while Th17 and Th1 cells exert a promoting effect.[34] Our study pointed that the HHV-6B-related antibody-mediated immune response acts as a protective factor against Gout. Consequently, we hypothesize that the protective mechanism might be inducted by an immune escape process mediated by HHV-6B Treg cells, resulting in a cascade of immunosuppressive effects. Nevertheless, the precise mechanisms necessitate further investigation in both in vitro and population-based studies.

Our research analysis found that immunity from JC polyomavirus (JCPyV) virus infection is a risk factor for Gout. VP1, the major capsid protein of JCPyV, is associated with immunodeficiency patients being more susceptible to the reactivation of the virus. Its infection is closely related to $CD4^+$ and $CD8^+$ T cells.[35,36] $CD8^+$ T cells differentiate into effector T cells with the assistance of $CD4^+$ T cells, and $CD8^+$ cytotoxic T lymphocytes can control viruses by eliminating the target cells.[37] The differentiation of both CD4T and CD8T is regulated by B cells.[38] Research has found the increase in $CD8^+$ T cell expression within the synovial tissue of individuals suffering from Gout.[39] GuH et al

Table 5 MR Results of Causal Effects Between Gout and Antibody-Mediated Immune Responses

GWAS id	Exposure	Outcome	Method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
finngen_R11_M13_GOUT	Gout	BK polyomavirus VP1 antibody levels	MR Egger	62	0.032506	0.041887	0.440778	−0.04959	0.114605	1.03304	0.951617	1.12143
finngen_R11_M13_GOUT	Gout	BK polyomavirus VP1 antibody levels	Weighted median	62	0.090426	0.037362	0.015508	0.017197	0.163655	1.094641	1.017346	1.177808
finngen_R11_M13_GOUT	Gout	BK polyomavirus VP1 antibody levels	Inverse variance weighted	62	0.055158	0.024551	0.024661	0.007038	0.103278	1.056708	1.007063	1.1088
finngen_R11_M13_GOUT	Gout	BK polyomavirus VP1 antibody levels	Simple mode	62	0.103415	0.07761	0.18765	−0.0487	0.25553	1.108952	0.952467	1.291146
finngen_R11_M13_GOUT	Gout	BK polyomavirus VP1 antibody levels	Weighted mode	62	0.094873	0.055763	0.093968	−0.01442	0.204169	1.099519	0.985681	1.226505
finngen_R11_M13_GOUT	Gout	Chlamydia trachomatis tarp-D F2 antibody levels	MR Egger	61	0.180206	0.087069	0.04287	0.00955	0.350862	1.197464	1.009596	1.420291
finngen_R11_M13_GOUT	Gout	Chlamydia trachomatis tarp-D F2 antibody levels	Weighted median	61	0.011004	0.082194	0.893496	−0.1501	0.172105	1.011065	0.860625	1.187803
finngen_R11_M13_GOUT	Gout	Chlamydia trachomatis tarp-D F2 antibody levels	Inverse variance weighted	61	0.106774	0.051417	0.037835	0.005997	0.207551	1.112683	1.006015	1.230661
finngen_R11_M13_GOUT	Gout	Chlamydia trachomatis tarp-D F2 antibody levels	Simple mode	61	0.101243	0.17722	0.569941	−0.24611	0.448594	1.106545	0.781838	1.566109
finngen_R11_M13_GOUT	Gout	Chlamydia trachomatis tarp-D F2 antibody levels	Weighted mode	61	0.063048	0.101953	0.538648	−0.13678	0.262876	1.065078	0.872162	1.300666
finngen_R11_M13_GOUT	Gout	Human herpes virus 6 p101k antibody levels	MR Egger	60	−0.11236	0.08867	0.210177	−0.28615	0.061438	0.893726	0.751151	1.063364
finngen_R11_M13_GOUT	Gout	Human herpes virus 6 p101k antibody levels	Weighted median	60	−0.0994	0.082133	0.226204	−0.26038	0.061583	0.905384	0.770762	1.063519
finngen_R11_M13_GOUT	Gout	Human herpes virus 6 p101k antibody levels	Inverse variance weighted	60	−0.10819	0.051839	0.036895	−0.20979	−0.00658	0.897461	0.810754	0.993442
finngen_R11_M13_GOUT	Gout	Human herpes virus 6 p101k antibody levels	Simple mode	60	−0.26638	0.179832	0.14386	−0.61885	0.086094	0.76615	0.538564	1.089909
finngen_R11_M13_GOUT	Gout	Human herpes virus 6 p101k antibody levels	Weighted mode	60	−0.23667	0.137726	0.09097	−0.50661	0.033276	0.789255	0.602536	1.033836
finngen_R11_M13_GOUT	Gout	Varicella zoster virus glycoproteins E and I antibody levels	MR Egger	62	0.014697	0.044402	0.741796	−0.07233	0.101725	1.014806	0.930223	1.107079
finngen_R11_M13_GOUT	Gout	Varicella zoster virus glycoproteins E and I antibody levels	Weighted median	62	0.045842	0.04089	0.262242	−0.0343	0.125986	1.046909	0.966279	1.134266
finngen_R11_M13_GOUT	Gout	Varicella zoster virus glycoproteins E and I antibody levels	Inverse variance weighted	62	0.059781	0.026027	0.021626	0.008768	0.110795	1.061604	1.008806	1.117165
finngen_R11_M13_GOUT	Gout	Varicella zoster virus glycoproteins E and I antibody levels	Simple mode	62	0.041516	0.073793	0.575768	−0.10312	0.186151	1.04239	0.90202	1.204604
finngen_R11_M13_GOUT	Gout	Varicella zoster virus glycoproteins E and I antibody levels	Weighted mode	62	0.041516	0.051685	0.424949	−0.05979	0.142819	1.04239	0.941965	1.153521

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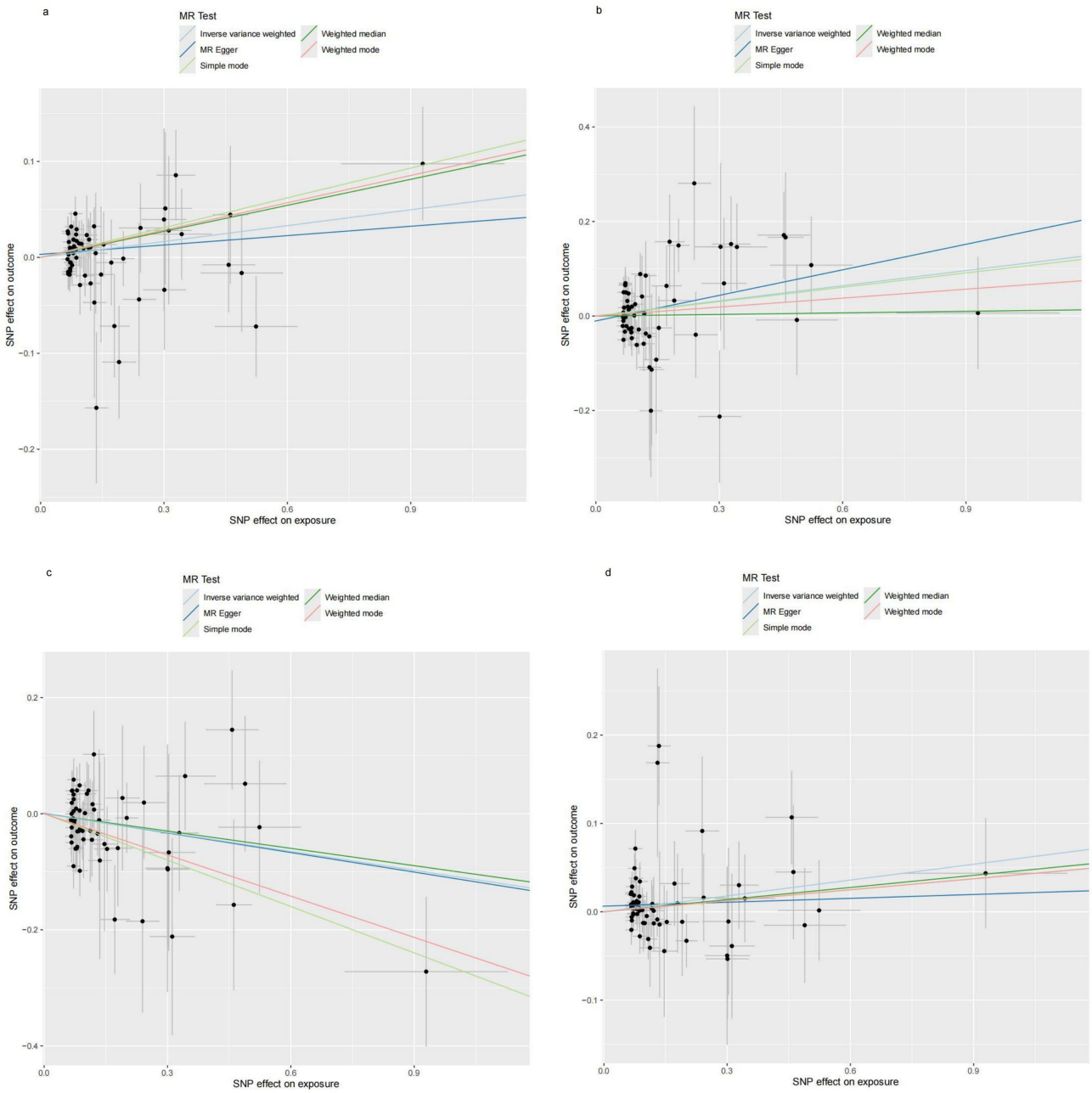

Figure 12 Scatter plots for the effect of Gout on antibody-mediated immune responses. (**a**) Analysis for "Gout" on "BK polyomavirus VP1 antibody levels". (**b**) Analysis for "Gout" on "Chlamydia trachomatis tarp-D F2 antibody levels". (**c**) Analysis for "Gout" on "Human herpes virus 6 p101k antibody levels". (**d**) Analysis for "Gout" on "Varicella zoster virus glycoproteins E and I antibody levels".
Abbreviation: SNP, single-nucleotide polymorphism.

discovered that hyperactivated CD8T could be a primary mechanism for the deposition of MSU crystals, contributing to the development of Gout.[40] This aligns with our findings. These results underscore the connection between JCPyV and Gout, indicating that preventing JCPyV may help to reduce the onset of Gout. However, the specific molecular relationship between infection and disease is still not clearly elucidated and needs further exploration, which also provides a new direction to prevent Gout.

BK polyomavirus (BK PyV) is a member of polyomavirus family. The capsid protein VP1 is crucial in facilitating the viral entry into cells.[41] Our study found that the elevated levels of BK PyV antibody offer some protective effect against RA. Antibodies are mainly produced by B cells, and certain studies have indicated that B cells facilitate the emergence of

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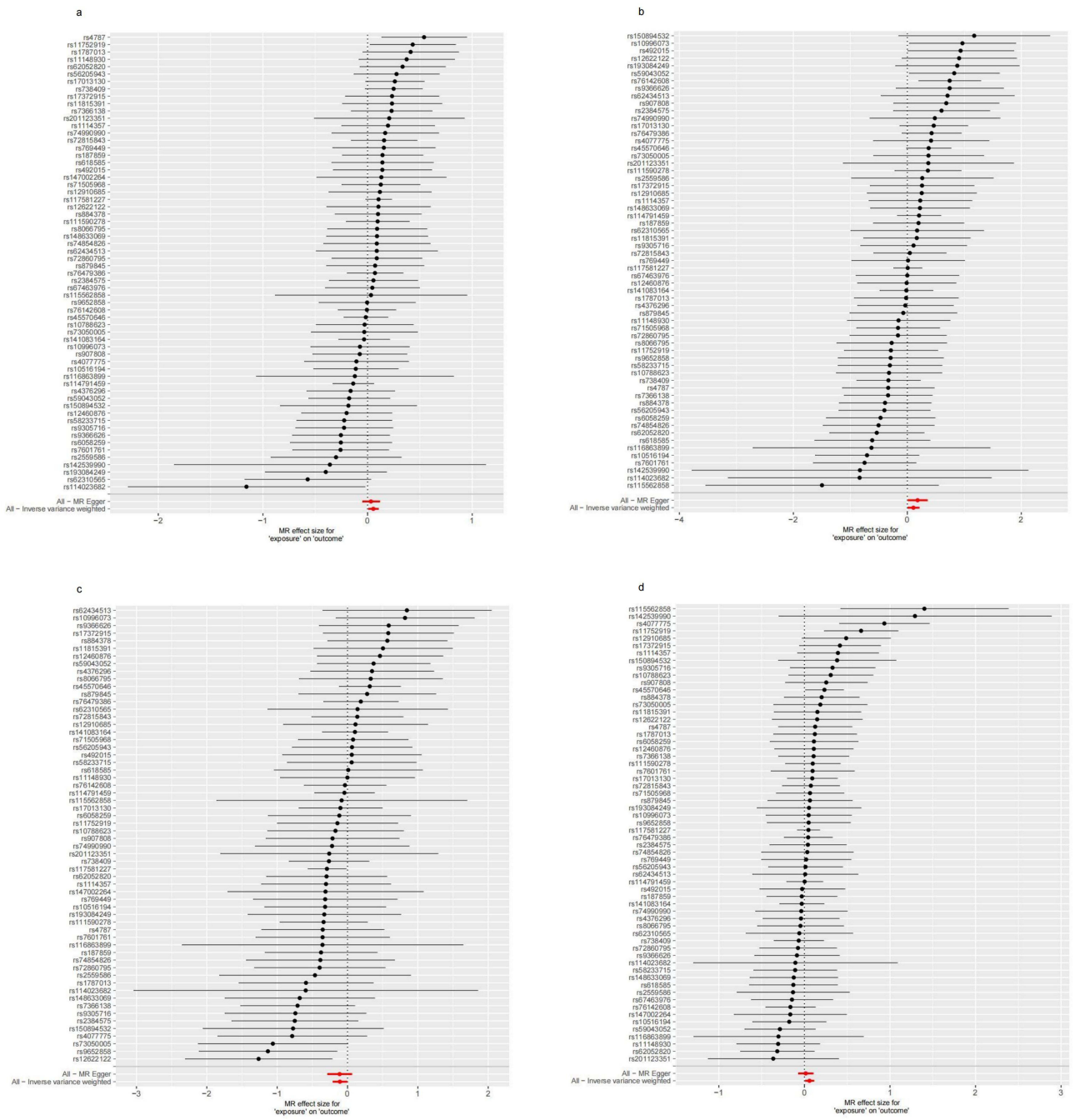

Figure 13 Forest plots for the effect of Gout on antibody-mediated immune responses. (**a**) Analysis for "Gout" on "BK polyomavirus VP1 antibody levels". (**b**) Analysis for "Gout" on "Chlamydia trachomatis tarp-D F2 antibody levels". (**c**) Analysis for "Gout" on "Human herpes virus 6 p101k antibody levels". (**d**) Analysis for "Gout" on "Varicella zoster virus glycoproteins E and I antibody levels".
Abbreviation: SNP, single-nucleotide polymorphism.

Treg cells.[42–44] Treg cells can maintain immune self-tolerance, effectively inhibit the proliferation of effector cells, and secrete IL-10 and TGF- β. Moreover, Treg cells can exert bystander inhibition by non-specific suppressing immune response against non-cognate antigens.[45] They can also specifically infiltrate inflammatory sites such as synovium.[46] Some studies have used the adoptive transfer of polyclonal Treg cells to treat autoinflammatory diseases and reduce the incidence of the disease.[47–49] This also suggests that we could focus more on this immunotherapy mechanism.

Table 6 Mendelian Randomization Sensitivity Analysis of Gout and RA

GWAS id	Exposure	Outcome	Pleiotropy Test				Heterogeneity test		
			MR Egger			MR-PRESSO			
			Intercept	SE	*P*-value		Method	Cochran's Q Statistic	*P*-Value
finngen_R11_M13_GOUT	Gout	BK polyomavirus VP1 antibody levels	0.003187	0.004775	0.507034	0.6416667	MR Egger	55.8024195	0.629767
							Inverse variance weighted	56.24792928	0.648449
finngen_R11_M13_GOUT	Gout	Chlamydia trachomatis tarp-D F2 antibody levels	−0.01042	0.009975	0.300459	0.272	MR Egger	64.91381645	0.278219
							Inverse variance weighted	66.11443245	0.274031
finngen_R11_M13_GOUT	Gout	Human herpes virus 6 p101k antibody levels	0.000591	0.010189	0.953972	0.6293333	MR Egger	54.51555479	0.605641
							Inverse variance weighted	54.51891535	0.641187
finngen_R11_M13_GOUT	Gout	Varicella zoster virus glycoproteins E and I antibody levels	0.006347	0.005065	0.214977	0.5106667	MR Egger	59.14099085	0.507107
							Inverse variance weighted	60.71162289	0.486328
finngen_R11_M13_RHEUMA	RA	Chlamydia trachomatis pGP3 antibody levels	−0.00227	0.009144	0.804083	0.3193333	MR Egger	82.70031518	0.720777
							Inverse variance weighted	82.76221188	0.743976
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 6 IE1A IgG seropositivity	0.011932	0.012621	0.346966	0.002333333	MR Egger	135.7593872	0.001649
							Inverse variance weighted	137.0927394	0.001614
finngen_R11_M13_RHEUMA	RA	Human herpes virus 6 IE1A antibody levels	0.00323	0.005896	0.585169	0.001666667	MR Egger	136.9854993	0.001314
							Inverse variance weighted	137.4372298	0.001515
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 7 IgG seropositivity	0.024139	0.019576	0.220724	0.483	MR Egger	91.570433	0.463503
							Inverse variance weighted	93.10043517	0.448312
finngen_R11_M13_RHEUMA	RA	Merkel cell polyomavirus VP1 antibody levels	−0.00781	0.005483	0.157796	0.2056667	MR Egger	100.973904	0.222757
							Inverse variance weighted	103.2246997	0.199127

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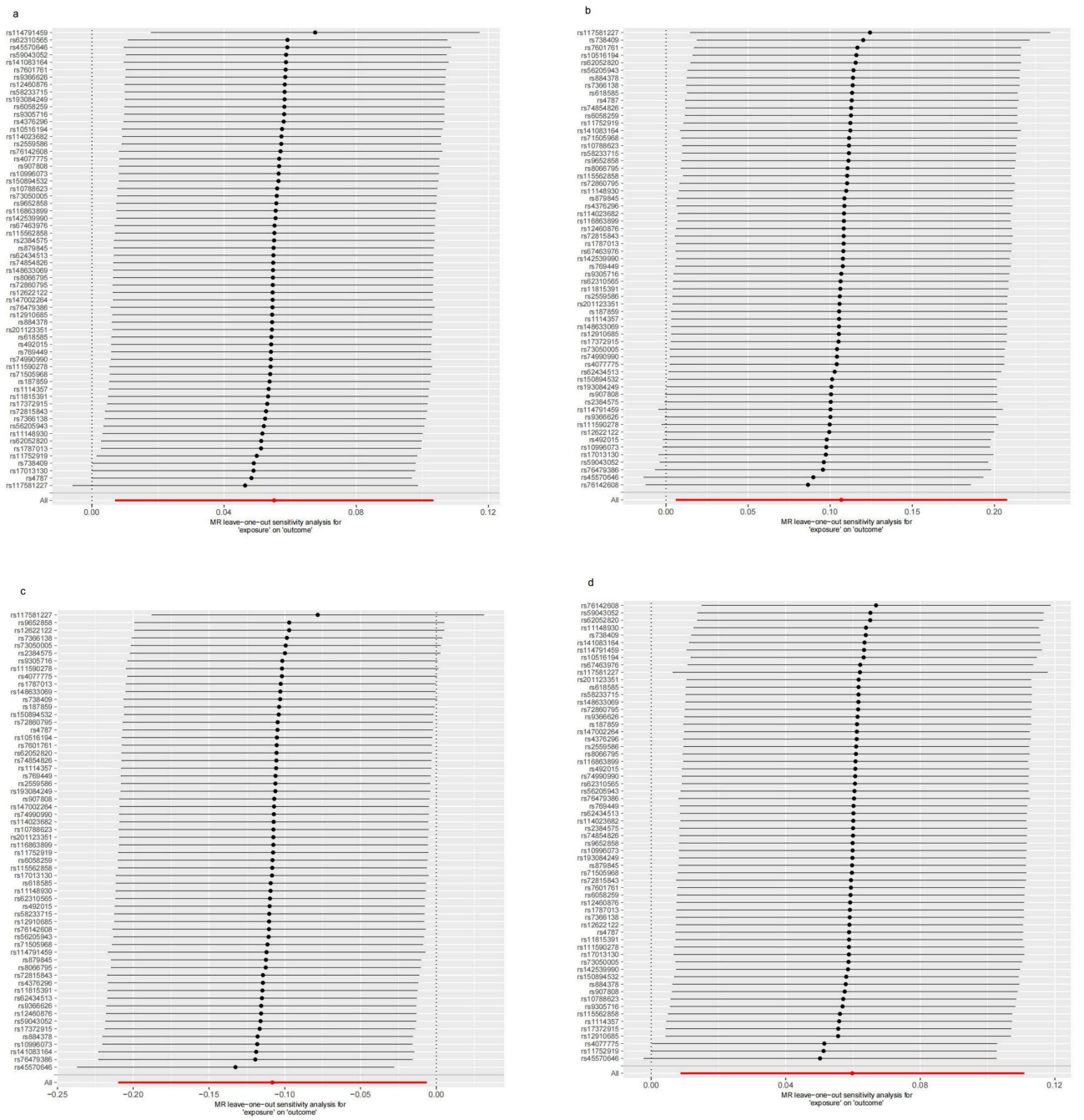

Figure 14 Leave-one-out sensitivity analysis for Gout on antibody-mediated immune responses. (**a**) Analysis for "Gout" on "BK polyomavirus VP1 antibody levels". (**b**) Analysis for "Gout" on "Chlamydia trachomatis tarp-D F2 antibody levels". (**c**) Analysis for "Gout" on "Human herpes virus 6 p101k antibody levels". (**d**) Analysis for "Gout" on "Varicella zoster virus glycoproteins E and I antibody levels".
Abbreviation: MR, Mendelian randomization.

On the other hand, Gout will elevate the increase in BK PyV, Chlamydia trachomatis tarp-D F2 antibody levels. RA leads to elevated increased Merkel cell polyomavirus VP1 antibody levels. This finding suggests that the two non-infectious inflammatory joint diseases play a certain modulatory role on the systemic immune response, potentially impacting the progression of certain infectious diseases. While there is no conclusive evidence to establish a clear association, and further research is needed to clarify the relationship.

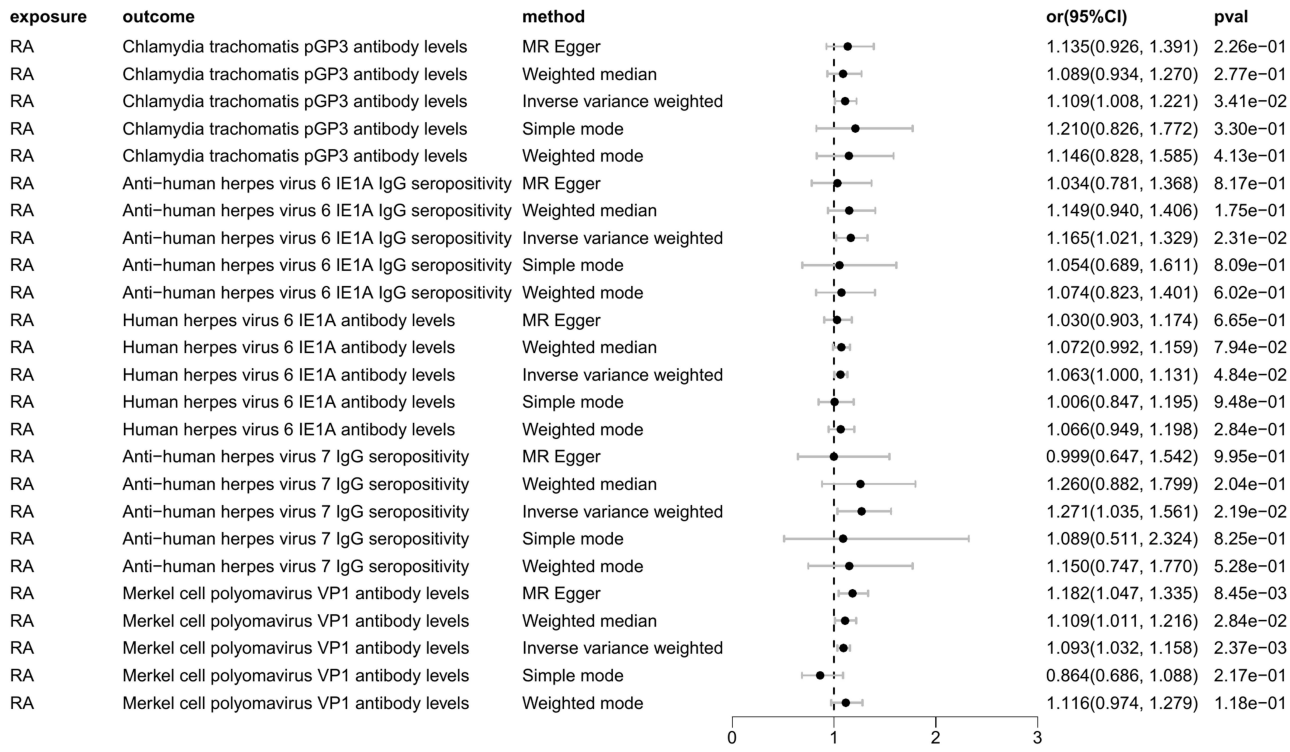

Figure 15 Forest plot visualization of the causal effect of RA on antibody-mediated immune responses.
Abbreviations: or, odds ratio; CI, confidence interval; RA, Rheumatoid Arthritis.

We have innovatively discovered that antibodies to infectious diseases may be related to Gout and RA, which will draw the attention of clinicians in the diagnosis and treatment of related diseases. For instance, patients infected with Polyomavirus 2 JC VP1 are more prone to Gout, and these patients may need to strictly control uric acid and diet. Anti-human herpes virus 6 IE1B IgG seropositivity and BK polyomavirus VP1 antibody levels can be somewhat helpful in preventing Gout and RA, but there are currently no vaccines available related to HHV-6B and BKPyV. This also calls for more scholars to actively engage in vaccine research and development. Gout and RA can also cause an increase in antibodies for certain infectious diseases, indicating that the likelihood of patients with Gout or RA contracting these diseases is reduced. This discovery updates our understanding and can assist clinicians in conducting preliminary exclusionary diagnoses for related patients.

In addition to the aforementioned relatively stable and significant findings, the IVW analysis results also indicated several secondary significant outcomes. In the forward MR analysis, anti-Chlamydia trachomatis IgG seropositivity and Helicobacter pylori GroEL antibody levels were identified as protective factors for Gout, reducing its likelihood of occurrence. While Helicobacter pylori Catalase antibody levels served as a protective factor for RA, decreasing the probability of its development. In the reverse MR analysis, Gout episodes may elevate Varicella zoster virus glycoproteins E and I antibody levels, and the onset of RA might increase Anti-human herpes virus 7 IgG seropositivity. Since these results only demonstrated significance under IVW analysis, we still need to maintain a cautious attitude when interpreting these results, and further animal or clinical studies are necessary to validate these conclusions.

Limitations does have in this study. First, the GWAS datasets were selected from individuals of European ancestry, which means there is a lack of analysis pertaining to Asia, Africa and other populations. Consequently, the findings are not universally applicable and necessitate additional research and analysis to confirm their validation. Second, when screening for IVs, we adopted the less strict threshold of $P < 5\times10^{-6}$ due to the insufficient of SNPs. This may impacted the estimated causal effects, so we anticipate incorporating more complete statistics and verification in future experiments to make the result analysis more reliable. In addition, the GWAS of Gout and RA did not clearly discriminate their onset

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Table 7 MR Results of Causal Effects Between RA and Antibody-Mediated Immune Responses

GWAS id	Exposure	Outcome	Method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
finngen_R11_M13_RHEUMA	RA	Chlamydia trachomatis pGP3 antibody levels	MR Egger	93	0.126525	0.103874	0.22635	−0.07707	0.330117	1.134877	0.925827	1.391132
finngen_R11_M13_RHEUMA	RA	Chlamydia trachomatis pGP3 antibody levels	Weighted median	93	0.085302	0.078517	0.277296	−0.06859	0.239195	1.089046	0.933708	1.270226
finngen_R11_M13_RHEUMA	RA	Chlamydia trachomatis pGP3 antibody levels	Inverse variance weighted	93	0.103732	0.048954	0.034094	0.007782	0.199682	1.109303	1.007812	1.221014
finngen_R11_M13_RHEUMA	RA	Chlamydia trachomatis pGP3 antibody levels	Simple mode	93	0.190644	0.194511	0.329598	−0.1906	0.571886	1.210028	0.826465	1.771605
finngen_R11_M13_RHEUMA	RA	Chlamydia trachomatis pGP3 antibody levels	Weighted mode	93	0.136257	0.165598	0.412739	−0.18831	0.460828	1.145976	0.828354	1.585386
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 6 IE1A IgG seropositivity	MR Egger	93	0.03316	0.143133	0.817313	−0.24738	0.3137	1.033716	0.780844	1.368479
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 6 IE1A IgG seropositivity	Weighted median	93	0.139193	0.102663	0.175156	−0.06203	0.340412	1.149346	0.939858	1.405527
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 6 IE1A IgG seropositivity	Inverse variance weighted	93	0.152627	0.067176	0.023082	0.020963	0.284292	1.164891	1.021185	1.32882
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 6 IE1A IgG seropositivity	Simple mode	93	0.052428	0.216577	0.80926	−0.37206	0.47692	1.053827	0.689311	1.611104
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 6 IE1A IgG seropositivity	Weighted mode	93	0.070986	0.135725	0.602223	−0.19503	0.337006	1.073566	0.822806	1.400748
finngen_R11_M13_RHEUMA	RA	Human herpes virus 6 IE1A antibody levels	MR Egger	93	0.029087	0.06705	0.665455	−0.10233	0.160504	1.029514	0.902731	1.174102
finngen_R11_M13_RHEUMA	RA	Human herpes virus 6 IE1A antibody levels	Weighted median	93	0.069604	0.039684	0.079435	−0.00818	0.147384	1.072083	0.991857	1.158799
finngen_R11_M13_RHEUMA	RA	Human herpes virus 6 IE1A antibody levels	Inverse variance weighted	93	0.061565	0.031192	0.048411	0.000429	0.122702	1.0635	1.000429	1.130548
finngen_R11_M13_RHEUMA	RA	Human herpes virus 6 IE1A antibody levels	Simple mode	93	0.005709	0.087819	0.948308	−0.16642	0.177834	1.005725	0.846694	1.194626
finngen_R11_M13_RHEUMA	RA	Human herpes virus 6 IE1A antibody levels	Weighted mode	93	0.064102	0.059502	0.284164	−0.05252	0.180726	1.066201	0.948833	1.198087
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 7 IgG seropositivity	MR Egger	93	−0.00131	0.221781	0.995291	−0.436	0.433378	0.998688	0.646616	1.542459
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 7 IgG seropositivity	Weighted median	93	0.231155	0.181811	0.203586	−0.12519	0.587504	1.260054	0.882325	1.799492
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 7 IgG seropositivity	Inverse variance weighted	93	0.239961	0.104701	0.021914	0.034746	0.445175	1.271199	1.035357	1.560764
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 7 IgG seropositivity	Simple mode	93	0.085602	0.386653	0.825277	−0.67224	0.843442	1.089373	0.510565	2.324355
finngen_R11_M13_RHEUMA	RA	Anti-human herpes virus 7 IgG seropositivity	Weighted mode	93	0.139636	0.220192	0.527553	−0.29194	0.571213	1.149855	0.746813	1.770413
finngen_R11_M13_RHEUMA	RA	Merkel cell polyomavirus VP1 antibody levels	MR Egger	93	0.167371	0.062169	0.008449	0.04552	0.289222	1.182192	1.046572	1.335388
finngen_R11_M13_RHEUMA	RA	Merkel cell polyomavirus VP1 antibody levels	Weighted median	93	0.10325	0.047121	0.02844	0.010893	0.195608	1.108769	1.010952	1.21605
finngen_R11_M13_RHEUMA	RA	Merkel cell polyomavirus VP1 antibody levels	Inverse variance weighted	93	0.089184	0.02934	0.002368	0.031679	0.14669	1.093282	1.032186	1.157995
finngen_R11_M13_RHEUMA	RA	Merkel cell polyomavirus VP1 antibody levels	Simple mode	93	−0.14633	0.117842	0.2175	−0.3773	0.084645	0.863876	0.685713	1.08833
finngen_R11_M13_RHEUMA	RA	Merkel cell polyomavirus VP1 antibody levels	Weighted mode	93	0.109635	0.06942	0.1177	−0.02643	0.245698	1.115871	0.973918	1.278514

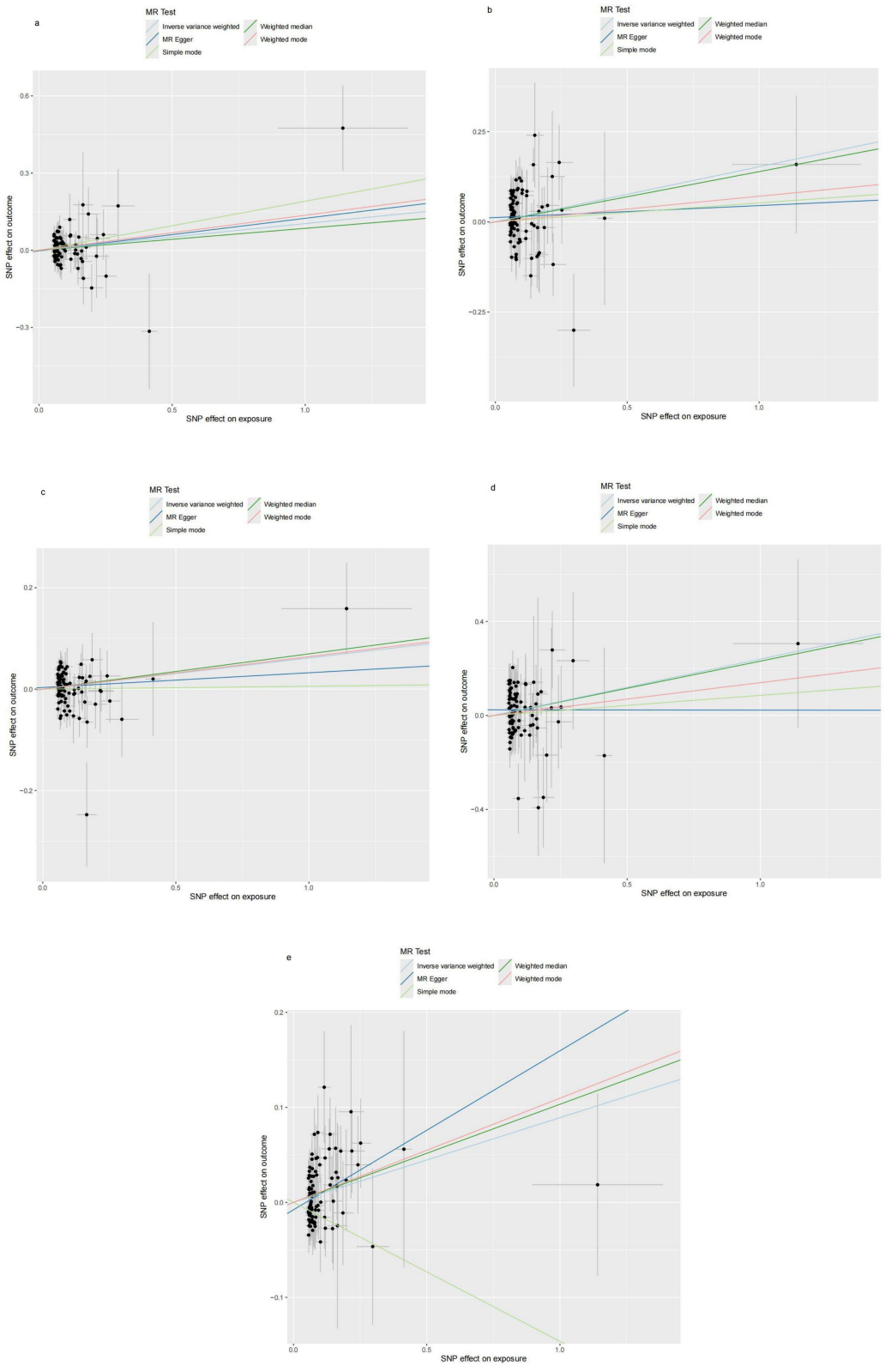

Figure 16 Scatter plots for the effect of RA on antibody-mediated immune responses. (**a**) Analysis for "RA" on "Chlamydia trachomatis pGP3 antibody levels". (**b**) Analysis for "RA" on "Anti-human herpes virus 6 IE1A IgG seropositivity". (**c**) Analysis for "RA" on "Human herpes virus 6 IE1A antibody levels". (**d**) Analysis for "RA" on "Anti-human herpes virus 7 IgG seropositivity" (**e**) Analysis for "RA" on "Merkel cell polyomavirus VP1 antibody levels".
Abbreviations: SNP, single-nucleotide polymorphism; RA, Rheumatoid Arthritis.

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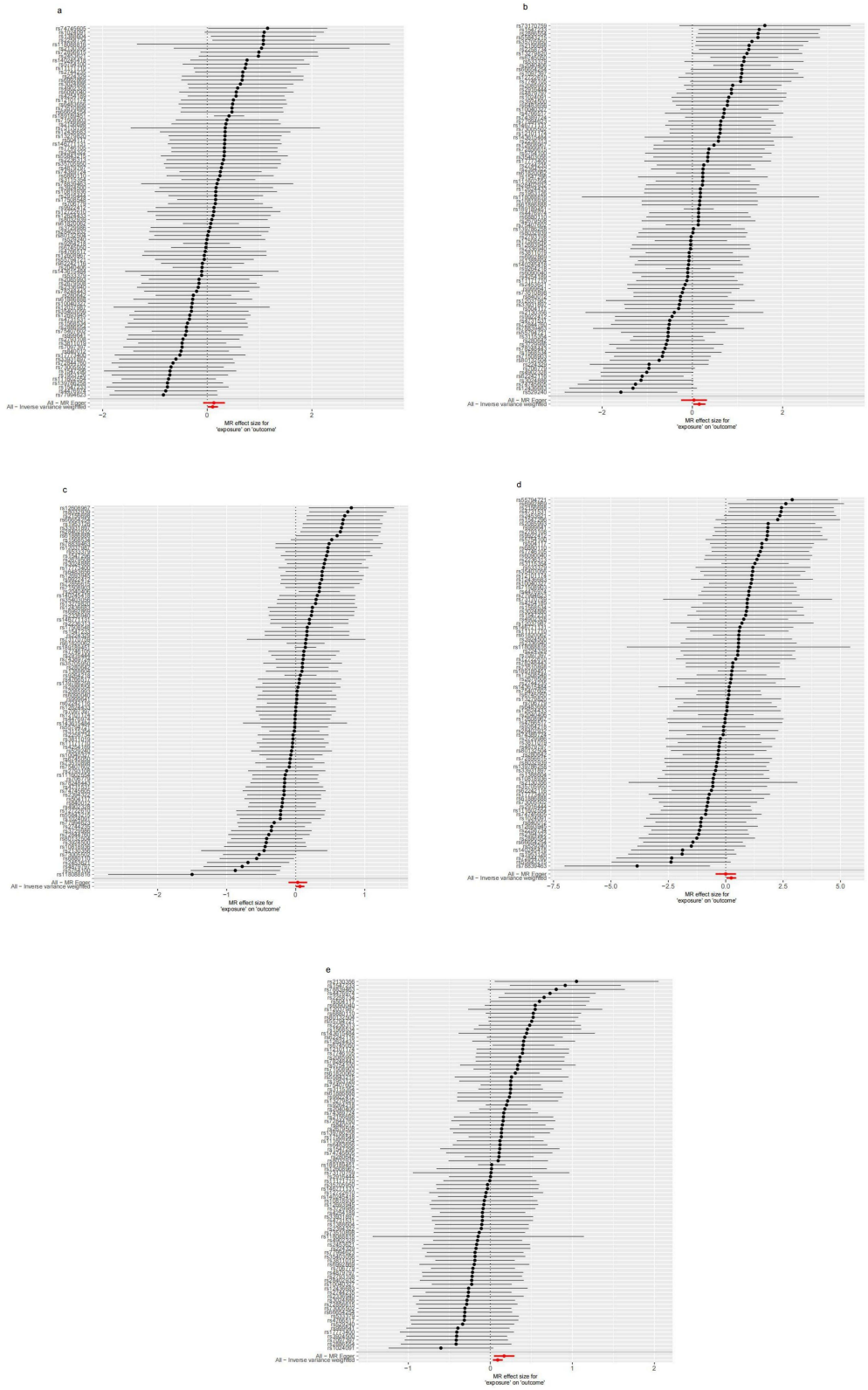

Figure 17 Forest plots for the effect of RA on antibody-mediated immune responses. (**a**) Analysis for "RA" on "Chlamydia trachomatis pGP3 antibody levels". (b) Analysis for "RA" on "Anti-human herpes virus 6 IE1A IgG seropositivity". (**c**) Analysis for "RA" on "Human herpes virus 6 IE1A antibody levels". (**d**), Analysis for "RA" on "Anti-human herpes virus 7 IgG seropositivity". (**e**) Analysis for "RA" on "Merkel cell polyomavirus VP1 antibody levels".
Abbreviations: SNP, single-nucleotide polymorphism; RA, Rheumatoid Arthritis.

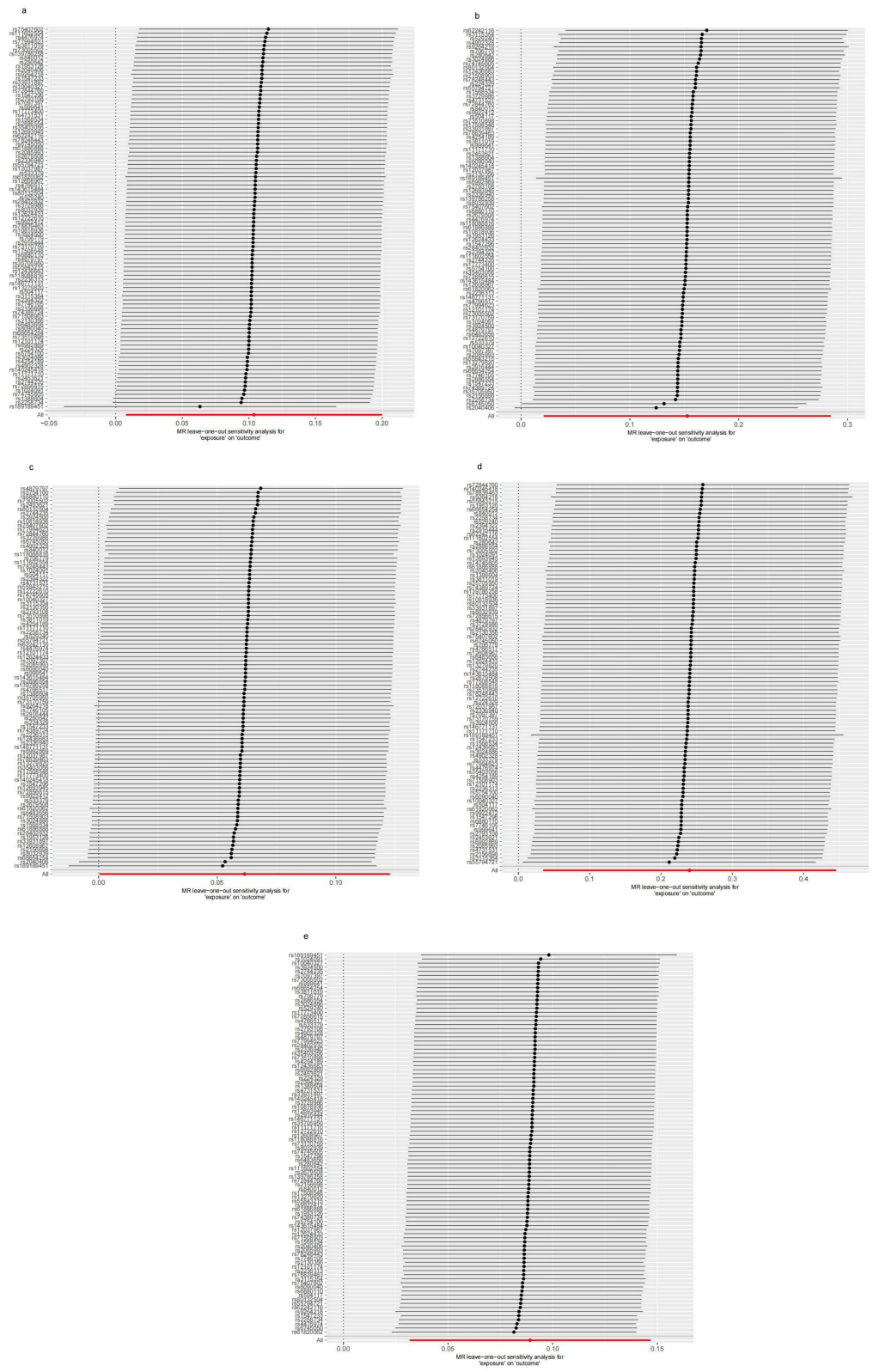

Figure 18 Leave-one-out sensitivity analysis for RA on antibody-mediated immune responses. (**a**) Analysis for "RA" on "Chlamydia trachomatis pGP3 antibody levels". (**b**) Analysis for "RA" on "Anti-human herpes virus 6 IE1A IgG seropositivity". (**c**) Analysis for "RA" on "Human herpes virus 6 IE1A antibody levels". (**d**) Analysis for "RA" on "Anti-human herpes virus 7 IgG seropositivity". (**e**) Analysis for "RA" on "Merkel cell polyomavirus VP1 antibody levels".
Abbreviation: MR, Mendelian randomization.

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and remission period, which hinders complete classification and may introduce bias into the results. Thus, the results should be interpreted with caution, and future experimental analyses may allow for stratified MR from the ictal and remission periods.

Conclusion

In conclusion, our study innovatively established a connection between infectious and non-infectious diseases, providing evidence for early screening of individuals at risk versus. We have finally identified 4 antibody-mediated immune responses that affect Gout, 2 antibody-mediated immune responses that influence RA, 3 antibody mediated immune responses influenced by Gout, and 2 antibody-mediated immune responses affected by RA. This proved that the antibody mediated immune responses are associated with these two non-infectious inflammatory joint diseases. Interestingly, we have found that different infectious antibodies may have varying causal effects on Gout. We propose an innovative conclusion that this may involve different immune mechanisms, including immune escape of HHV-6B and overactivation of JC polyomavirus CD8T cells. Our research findings provide new directions for future experiments, which can focus on the comorbidity and immunological perspectives, paying attention to immune escape mechanisms, CD8T cells, and Treg cells. Existing research reports are limited, and we hope to have further clinical observational studies or immunological research to support our findings and perspectives. In the results of the inverse relationship, there is no clear theoretical or experimental evidence to support our views, thus the impact of Gout and RA on infectious antibodies cannot be clearly defined at present. Future comparative experiments are needed to demonstrate whether patients with gout and RA are more likely to have high antibodies related to infectious diseases and the underlying immune mechanisms, which current research cannot explain.

Abbreviations

RA, Rheumatoid Arthritis; MR, Mendelian Randomization; GWAS, genome-wide association studies; IVW, Inverse Variance Weighted; MR-PRESSO, MR pleiotropy residual sum and outlier; IV, instrumental variable; RCT, randomized controlled trials; OR, odds ratio; CI, confidence intervals; HHV-6, Human herpes virus 6; DCs, dendritic cells; JCPyV, JC polyomavirus; BK PyV, BK polyomavirus.

Data Sharing Statement

Public databases used in this study are available at https://www.ebi.ac.uk/gwas/ and https://www.finngen.fi/en. The analysis data and results of this study are detailed in Table 1-7, Supplementary Tables 1 and 2, and Figures 1-18. Reasonable requests are supported, and data that supports the conclusion of this article can be obtained from the author (Zhouhanyu0604@163.com).

Ethics Approval and Consent to Participate

Our GWAS analysis study has been approved for exemption from ethical review by the IRB (Ethics Committee of Guangdong Provincial Hospital of Integrated Traditional and Western Medicine), and we have included a statement of approval in the attachment (details of ethics committee approval). According to the National Health Commission of the People's Republic of China, the Ministry of Education, the Ministry of Science and Technology, the State Administration of Traditional Chinese Medicine issued the "Notice on the issuance of Human Life Sciences and medical research ethical Review Measures" Article 32: Using legally available public data, or by observing and does not interfere with the study on the data of public behavior of exempt from ethical review (https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743658.htm).

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Disclosure

The authors declare that there is no potential conflict of interest in this study.

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